CHAPTER 8

Iodine and Iodine Compounds

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Iodine, a nonmetallic, essential element discovered in 1812 by the French scientist Courtois, was named by Gay-Lussac in 1814 after the Greek word meaning violet, which is the color of iodine vapor. It is not found in elemental form in nature but occurs sparingly in the form of iodides in seawater, from which it is assimilated by seaweeds; in Chilean saltpeter and nitrate-bearing earth, known as *caliche;* in brines from old sea deposits; and in brackish water from oil and salt wells. Besides the one stable isotope, ^{127}I, there are more than 30 artificial isotopes with half-lives between 0.2 second and 1.57×10^7 years. Some of them form a dangerous part of the uncontrolled emissions during nuclear accidents, whereas others are used in nuclear medicine [mainly ^{131}I (8.04 days) and ^{123}I (13.2 hours)].

So far as is known, the first use of iodine in medical practice was as a remedy for bronchocele (Halliday, 1821). Soon afterward, Lugol (1829) treated scrofuloderma (tuberculous lesions of the skin) with an iodine/iodide solution bearing his name that is still in use today (as Strong Iodine Solution, USP XXIII). The first specific reference to the use of iodine in wounds was made in 1839 (Davies, 1839; Boinet, 1865). Iodine was officially recognized by the *Pharmacopoeia of the United States* in 1830, specifically as *tinctura iodini* (tincture of iodine). The first fundamental papers with a scientific basis about the degerming efficacy of iodine were published from 1874 to 1881 by Davaine (Vallin, 1882). In 1874, he found iodine to be one of the most efficacious antiseptics, a notion that is still valid 125 years later. On the basis of Davaine's experience, Koch experimented with the disinfecting effect of iodine against anthrax spores. His results are contained in a comprehensive paper entitled *Desinfektion* (Koch, 1881). In the meantime, the literature about the use of iodine as a disinfectant has expanded markedly. Clinicians and microbiologists described a great number of experimental data and clinical applications, which can be found in numerous surveys (Reddish, 1957; Sykes, 1972; Bolek et al., 1972; Horn et al., 1972, 1974; Knolle, 1975; Gershenfeld, 1977).

Despite the successes that have been achieved with iodine, it was ascertained early that it also possesses properties unsuitable for practical application. Goebel (1906) referred to iodine's unpleasant odor; in addition, it stains the skin an intense yellowish-brown, causes blue stains in the laundry in the presence of starch, and combines with iron and other metals. Furthermore, its solutions are not stable (under certain circumstances), it irritates animal tissue, and it is a poison. The adverse side effects of iodine, its painfulness on open wounds, and the possibility of allergic reactions have in the past 100 years led to the development of a great many iodine-based preparations designed to avoid these incompatibilities without a significant loss of germicidal efficiency. The iodophors were the first such compounds largely to achieve this goal.

CHEMISTRY

Iodine, the halogen with the highest atomic weight (126.9) of the common halogens, forms grayish-black metallic scales that melt at 113.5°C to a black, mobile liquid. Iodine boils at 184.4°C at atmospheric pressure to produce the characteristic violet-colored vapor. In spite of the high boiling point, it already has an appreciable vapor pressure at room temperature and sublimes before it melts if it is not heated too fast and with too high a degree of heat.

Elemental iodine is only slightly soluble in water, forming a brown solution. Its solubility in water is increased with the addition of alkali iodides by which triiodide and higher polyiodides are formed [see equations (3), (5), and (6)]. In polar organic solvents (alcohols, ketones, carbonic

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acids), iodine forms a brown solution; in apolar solvents (CCl_4, benzene, hydrocarbons), it dissolves to a violet color. Whereas in the violet solutions, iodine is present as I_2 molecules (as in the gas phase), the brown color is explained by the formation of a compound between iodine and the solvent molecule (charge transfer complexes).

Properties of Disinfecting Iodine Solutions

Iodine-based disinfectants can be divided into three main groups according to the solvent and substances interfering (by complexing) with the iodine species: (a) pure aqueous solutions; (b) alcoholic solutions; and (c) iodophoric preparations, which exhibit intrinsic differences in their chemical and microbicidal properties. In addition, there are combined systems containing two or all three components.

A reliable understanding of the processes occurring at disinfection, which comprises not only killing of microorganisms but interactions with the material to be disinfected (e.g., innate surfaces, living tissue, body fluids) is essentially based on knowledge of the species occurring in the particular solvent, their equilibrium concentrations, and their individual reactivities. However, these features are only partially clear and, in addition, are of importance only for conditions in which interaction with reducing substances can be neglected.

Aqueous Solution

For the system iodine–water, nine different equilibria [equations (1) through (9)] are specified (Clough and Starke, 1985) that produce at least ten iodine species: I^-, I_2, I_3^-, I_5^-, I_6^{2-}, HOI, OI^-, HI_2O^-, I_2O^{2-}, H_2OI^+, and IO_3^-.

$$I_2 + H_2O \leftrightarrow HOI + I^- + H^+ \text{ (hydrolysis, } K_1) \quad (1)$$

$$HOI \leftrightarrow OI^- + H^+ \text{ (dissociation of HOI, } K_2) \quad (2)$$

$$I_2 + I^- \leftrightarrow I_3^- \text{ (triiodide formation, } K_3) \quad (3)$$

$$HOI + H^+ \leftrightarrow H_2OI^+ \text{ (protonization of HOI, } K_4) \quad (4)$$

$$I_3^- + I_2 \leftrightarrow I_5^- \text{ (pentaiodide formation, } K_5) \quad (5)$$

$$2I_3^- \leftrightarrow I_6^{2-} \text{ (dimerization of } I_3^-, K_6) \quad (6)$$

$$OI^- + I^- + H_2O \leftrightarrow HI_2O^- + OH^- \text{ (iodination of } OI^-, K_7) \quad (7)$$

$$HI_2O^- \leftrightarrow I_2O^- + H^+ \text{ (dissociation of } HI_2O^-, K_8) \quad (8)$$

$$3HOI \leftrightarrow IO_3^- + 2I^- + 3H^+ \text{ (disproportionation)} \quad (9)$$

As can be seen, this is a system of appreciable complexity, with several associated equilibria governed mainly by H^+ and I^- ions, which implies that pH and additional iodide influence equilibrium concentrations. Another important feature is the reaction rate: whereas the reactions in equations (1) through (8) are thought to run almost instantaneously, disproportionation to iodate [equation (9)] proceeds comparatively slowly, with a rate highly influenced by pH and additional iodide, as can easily be deduced from the rate law (Gottardi, 1981):

$$d[IO_3^-]/dt \approx 4 \times 10^{-38}[I_2]^3/[I^-]^3[H^+]^4 * \quad (10)$$

The brackets in equation (10) refer to the equilibrium concentration of the bracketed species. Because the reactions in equations (1) through (9) are well studied, with important contributions published since the early 1980s that focus on the fate of radioiodine species that emerge in the course of nuclear accidents (Clough and Starke, 1985), a calculation represents the easiest way to approach equilibrium concentrations, whereas experimentally it would require immense labor, quite apart from the fact that for some species no analytical methods are available (Gottardi, 1998).

Several investigations into the equilibrium concentrations of aqueous iodine solutions have been done; they differ mainly with regard to the equilibria considered and the regulating parameters, pH and additional iodide. One study investigated all the immediately established equilibria [equations (1) through (8)] and both regulating parameters (Gottardi, 1999). It dealt with fresh iodine solutions not altered by disproportionation (iodate formation) and provided results about the equilibrium concentrations of the species I^-, I_2, I_3^-, I_5^-, I_6^{2-}, HOI, OI^-, HI_2O^-, IO_2^-, and H_2OI^+. Its results for selected variations of total iodine and iodide, Lugol's solution and its dilutions, and the rates of iodate formation (Figs. 8.1 to 8.4) are the basis for most of the following conclusions:

- Additional iodide and pH have a very great influence (several orders of magnitude) on the individual equilibrium concentrations, and consequently conditions can be indicated in which the number of species of importance is drastically reduced. In the most common case, iodine in presence of additional iodide at pH 6 or less, only I^-, I_2, and I_3^- play a role (Fig. 8.2).
- In such a system, the analysis is fairly simple because HOI and all species derived from it (OI^-, HI_2O^-, I_2O^{2-}, H_2OI^+) and the higher polyiodides can be neglected without any noticeable loss of precision. In other words, in this case only the triiodide equilibrium [equation (3)] is relevant, and it is not influenced by pH. This has two consequences: (a) the distribution of the three species is the same at pH 6 or less; and (b) a sufficiently precise evaluation can be based solely on the determination of $[I_2]$ [e.g., potentiometrically (Gottardi, 1983) or by dialysis (Horn and Ditter, 1984)] and $[I^-]$ (iodide electrode), whereas triiodide is calculated from both. However, there also are methods that measure these species in a single operation (Gottardi, 1996, 1998).
- Exceptions for the above-quoted restriction to I^-, I_2, and I_3^- in presence of additional iodide are systems with very

*[ ] means equilibrium concentration of the bracketed species.

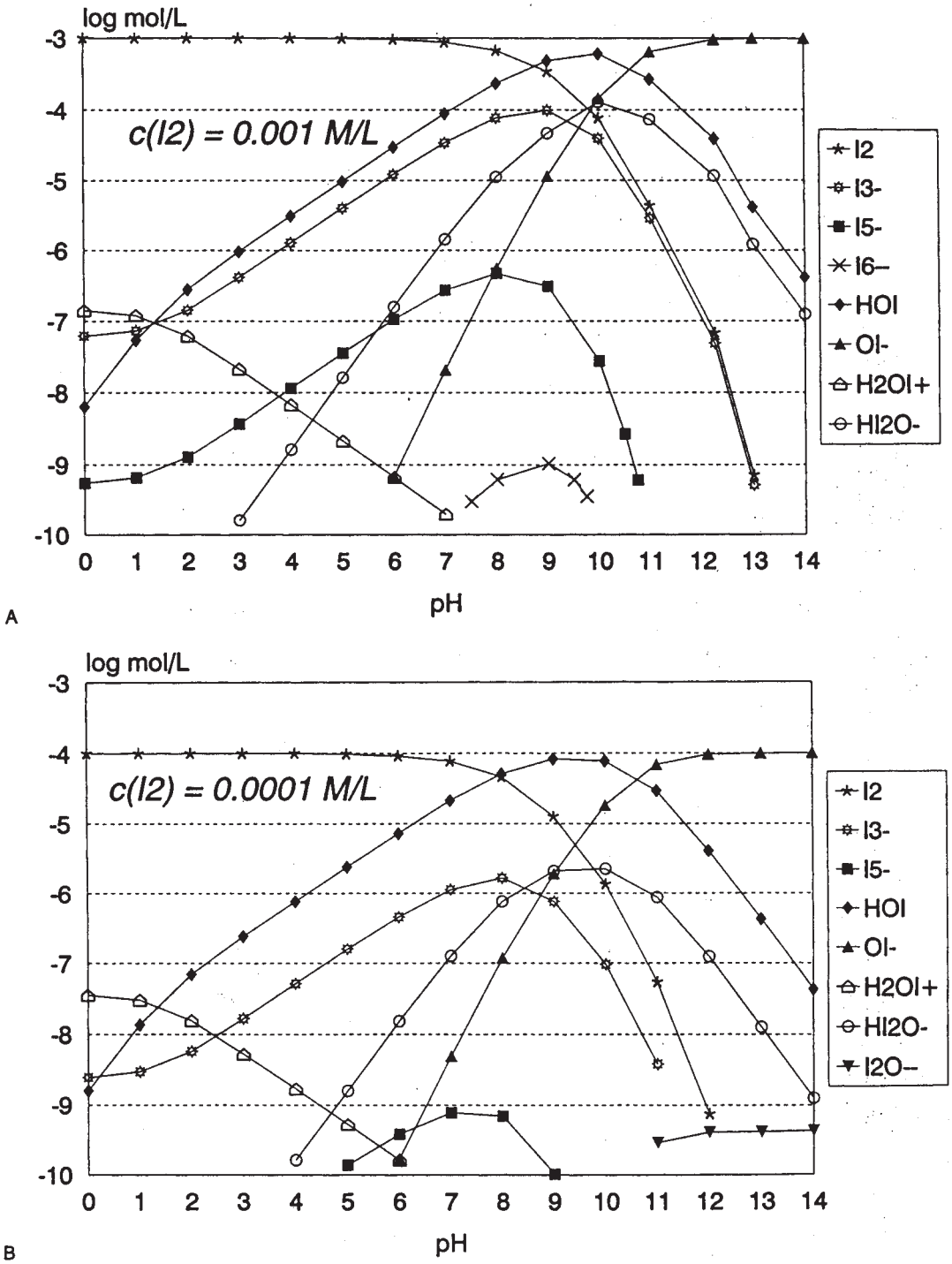

FIG. 8.1. Calculated equilibrium concentrations in aqueous iodine solutions without additional iodide. **A:** $c(I_2) = 10^{-3}$ mol/L. **B:** $c(I_2) = 10^{-4}$ mol/L.

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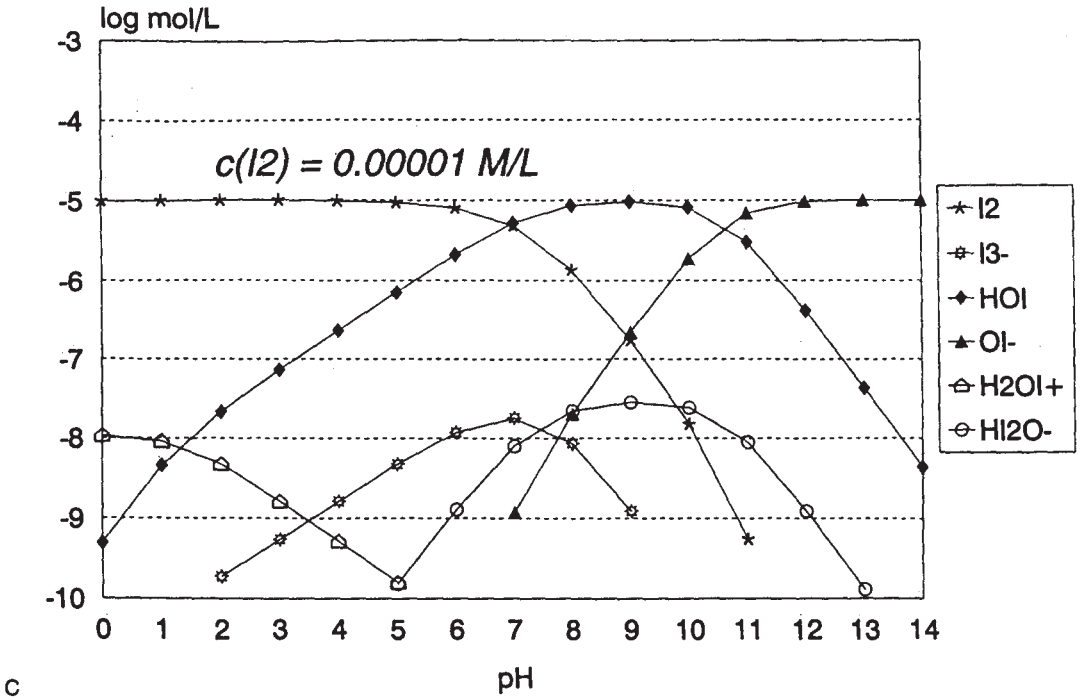

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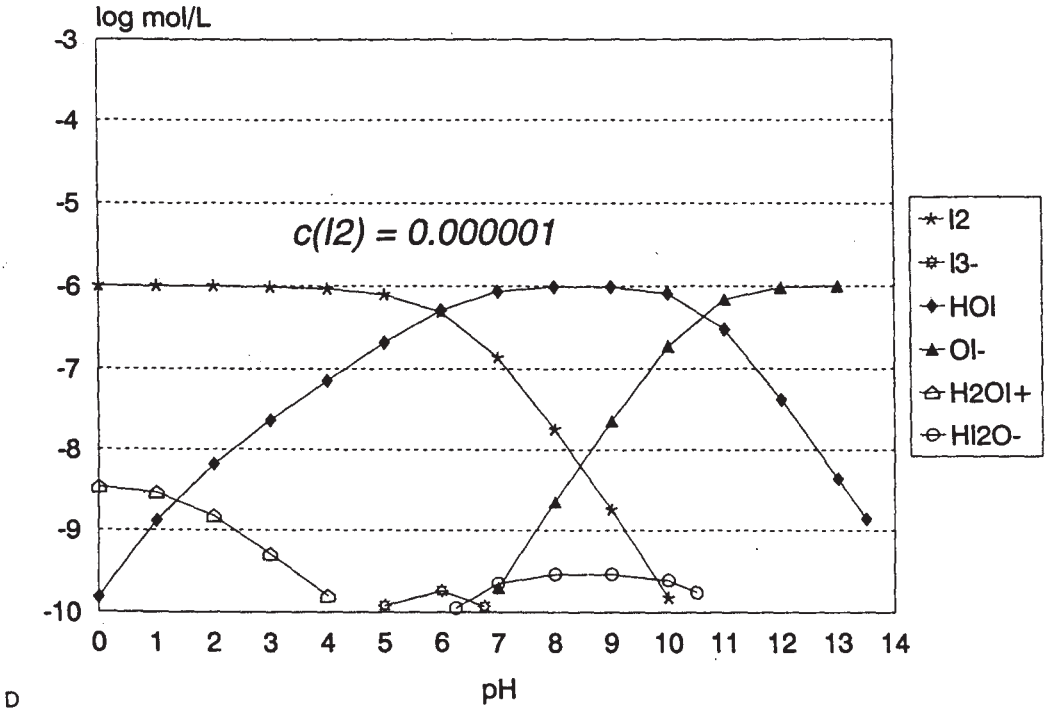

D

FIG. 8.1. *Continued.* **C:** $c(I_2) = 10^{-5}$ mol/L. **D:** $c(I_2) = 10^{-6}$ mol/L.

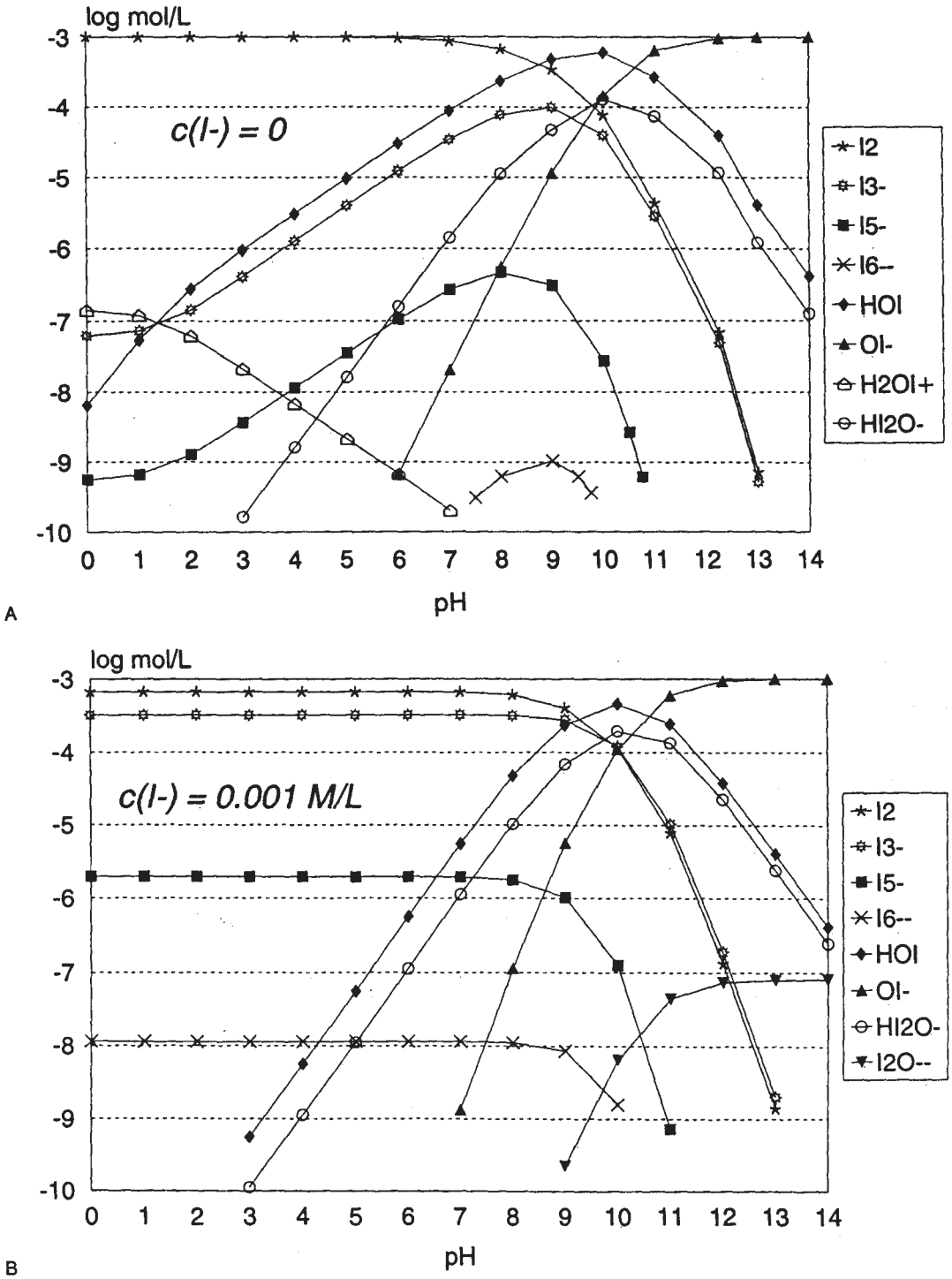

FIG. 8.2. Calculated equilibrium concentrations in aqueous 10^{-3} mol/L iodine solutions in presence of additional iodide. **A:** No additional iodide. **B:** $c(I^-) = 10^{-3}$ mol/L.

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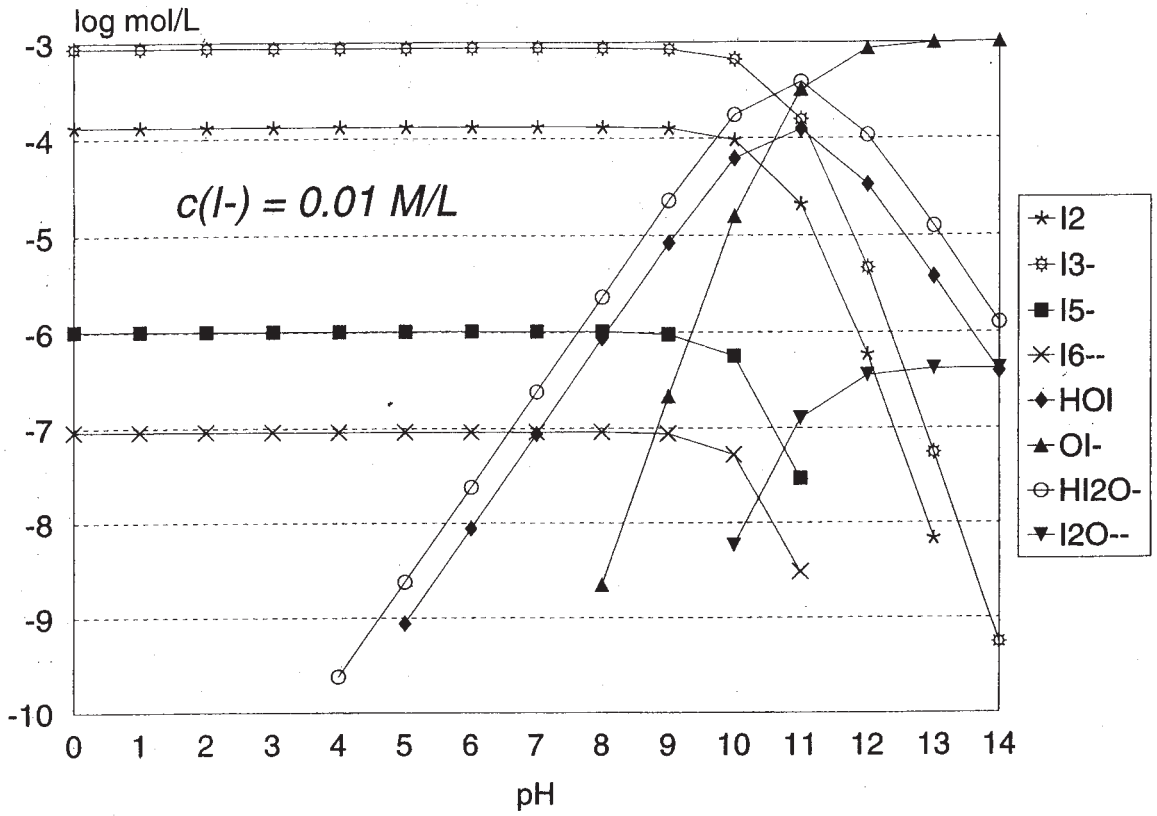

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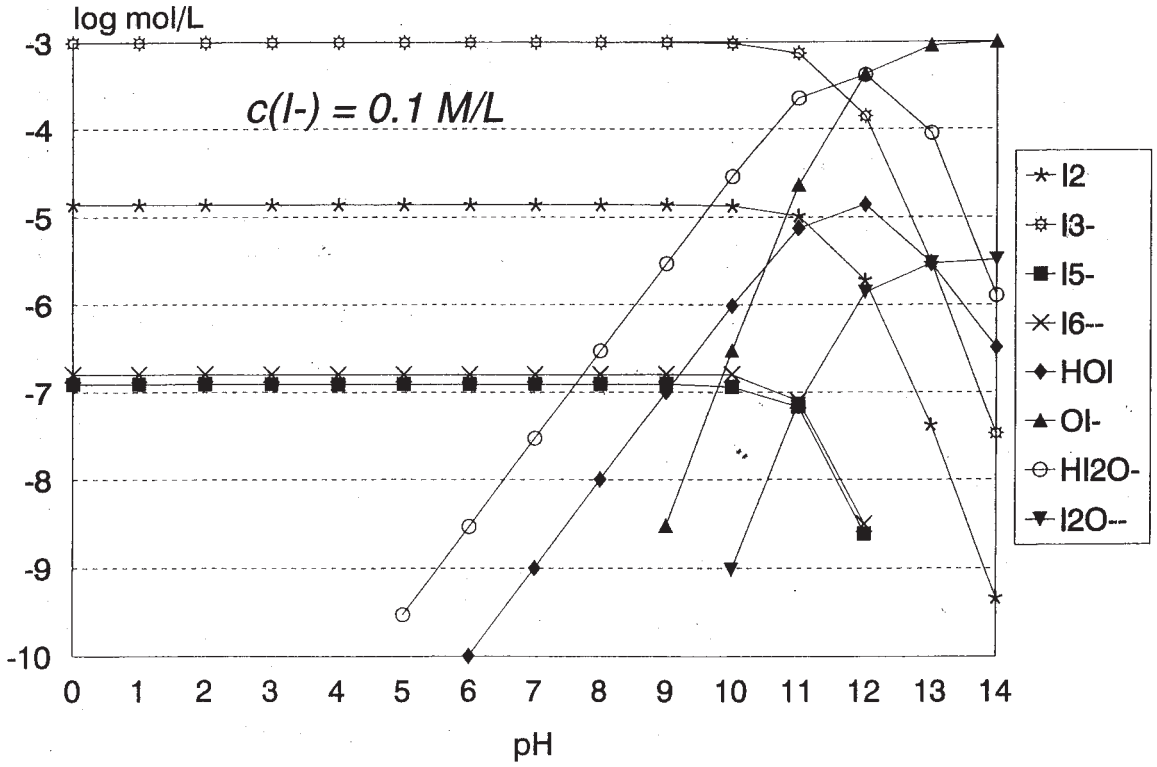

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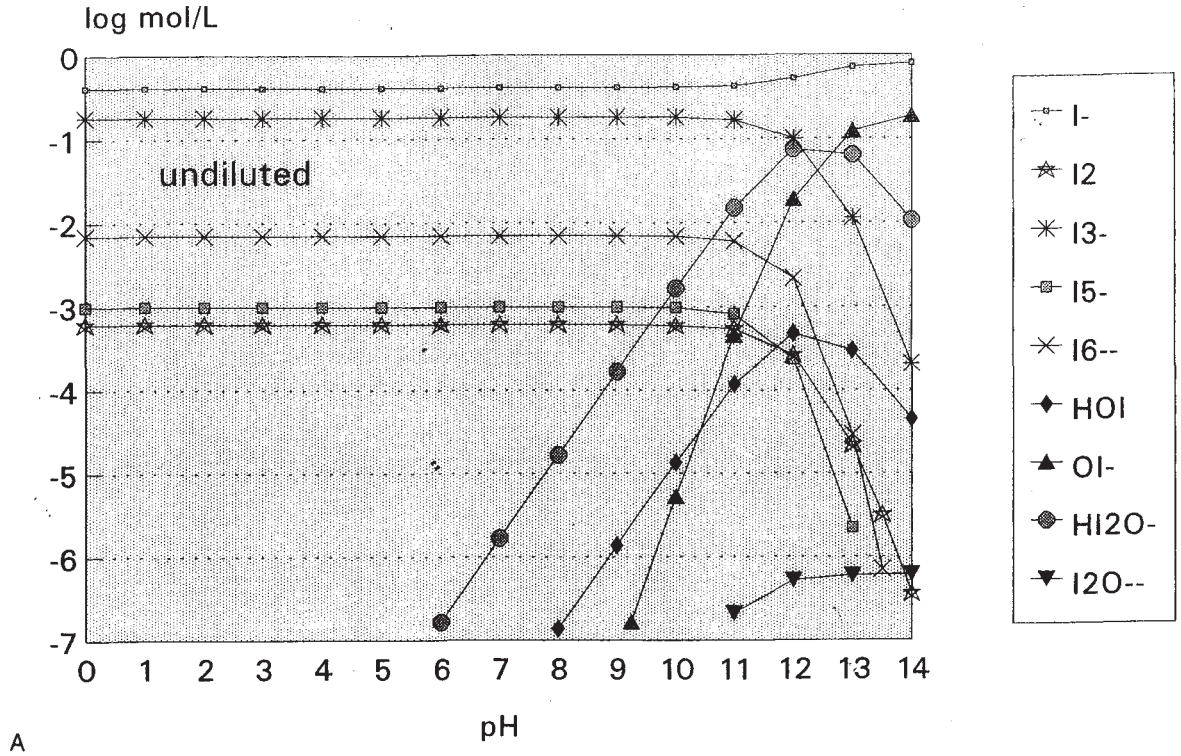
FIG. 8.2. *Continued.* **C:** $c(I^-) = 10^{-2}$ mol/L. **D:** $c(I^-) = 10^{-1}$ mol/L.



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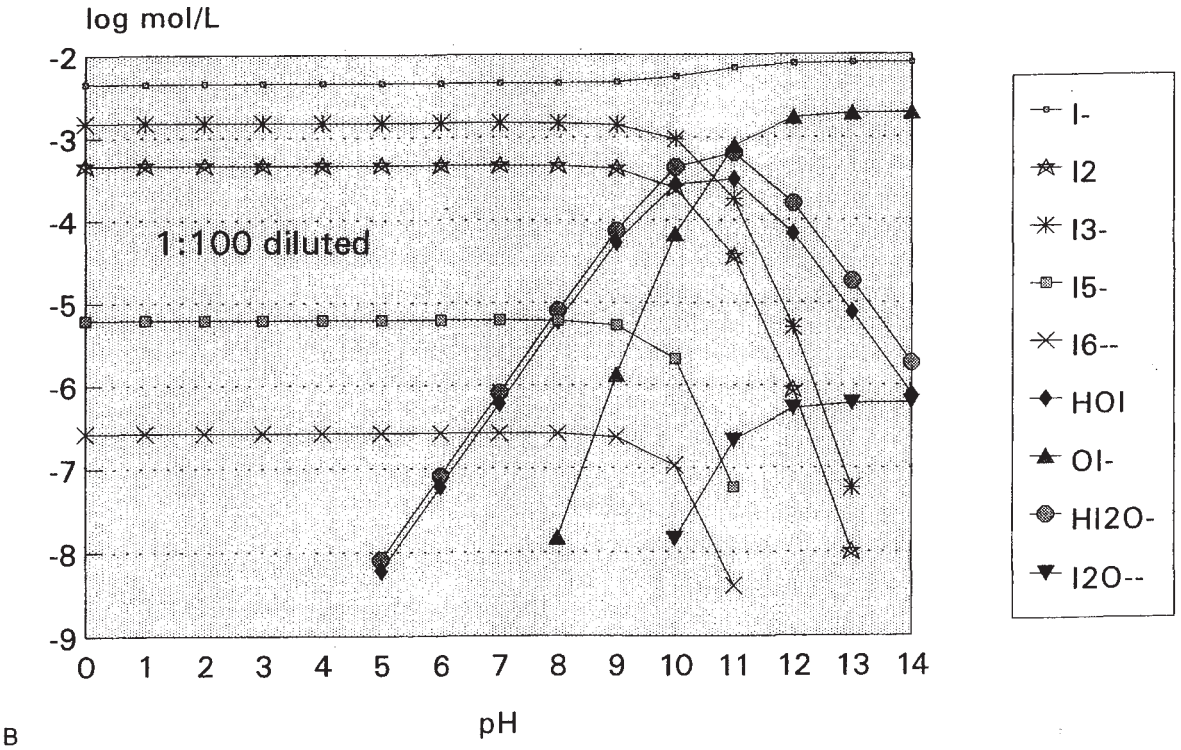

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FIG. 8.3. Calculated equilibrium concentrations in Lugol's solution and its dilutions. **A:** Undiluted. **B:** 1 : 100.

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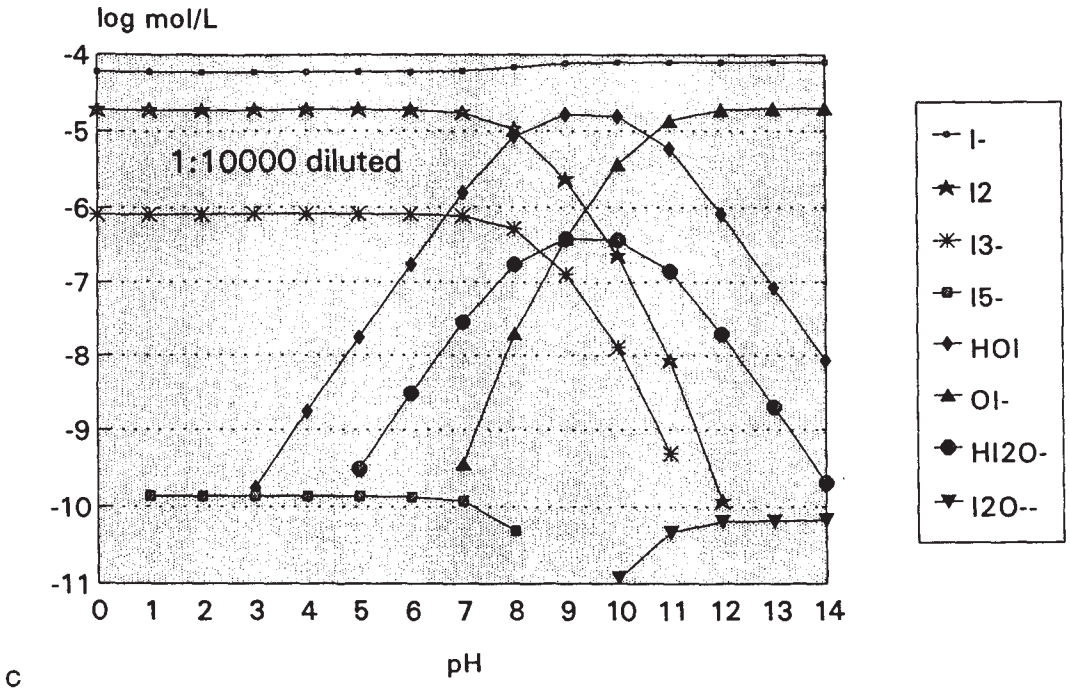

C

FIG. 8.3. *Continued.* **C:** 1 : 10,000.

high iodide *and* iodine concentrations in which the equilibria in equations (5) and (6) also are important, but which are independent of pH as is the case with the equilibrium in equation 3. For example, in high-level Lugol's solution, the species I_5^- and I_6^{2-} make up 8.2% of the oxidation capacity and should not be neglected (Fig. 8.3A).

On the other hand, in the absence of additional iodide, at pH 8 to 9 and at high dilution [$c(I_2) \leq 10^{-5}$ mol/L], HOI accounts for over 90% of the oxidation capacity (Fig. 8.1C,D). Absence of iodide also is obligatory for the presence of the iodine cation H_2OI^+ (Bell and Gelles, 1951), but in an extremely acid milieu that is without any relevance for practice (see later).

The problem of stability (i.e., rate of iodate formation) arising at pH above 7 can be reduced to the equilibrium concentration of hypoiodous acid, which manifests in the simple rate law:

$$d[IO_3^-]/dt = 0.25[HOI]^3/H^+]$$

which allows an estimation of stability at weak alkaline conditions (Gottardi, 1999). Figure 8.4 shows the initial rates of iodate formation (as a measure of stability) for iodine solutions (10^{-6} to 10^{-3} mol/L) without additional iodide, and for a 0.001 mol/L iodine solution in the presence of additional iodide (10^{-4} to 10^{-1} mol/L; see also Stability of Iodine-based Disinfectants, later).

The poor solubility of elemental iodine in water (338.3 ppm, 25°C, pH 5) can be increased by addition of iodide. This feature was first used by Lugol (1829), to whom we owe the well known disinfecting solution bearing his name. Lugol's solution is a high-concentration iodine formulation with 5% iodine (0.197 mol/L) and 10% KI (0.6024 mol/L) and the following equilibrium concentrations: $6.129e^{-4}$ mol/L (155.6 ppm) free molecular iodine, 0.1803 mol/L (68,640 ppm) triiodide, 9.95×10^{-4} mol/L (631 ppm) pentaiodide, 7.03×10^{-3} mol/L (5,350 ppm) hexaiodide, and 0.406 mol/L (51,650 ppm) iodide. Lugol's solution, with a threefold molar excess of iodide, is completely soluble at any dilution. This applies to all iodine/iodide ratios at least down to a twofold excess of iodide. Less iodide results in a gap of solubility of free molecular iodine.

Alcoholic Solution

Iodine equilibrates with alcohols by undergoing "outer" and "inner" complexes that finally result in the formation of triiodide, a reaction accomplished after approximately 24 hours (Bhattacharjee et al., 1983):

$$ROH + I_2 \leftrightarrow \underset{\text{"outer complex"}}{ROH \cdot I_2} \leftrightarrow \underset{\text{"inner complex"}}{ROHI^+I^-} \leftrightarrow ROHI^+ I^-$$

$$I_2 + I^- \leftrightarrow I_3^-$$

$$I_3^- + ROH \leftrightarrow ROH \cdot I_3^-$$

Therefore, as in the aqueous system, we have several oxidizing iodine species: I_2, $ROH{\cdot}I_2$, $ROHI^+$, I_3^- and $ROH{\cdot}I_3^-$. Calculations concerning their distribution, how-

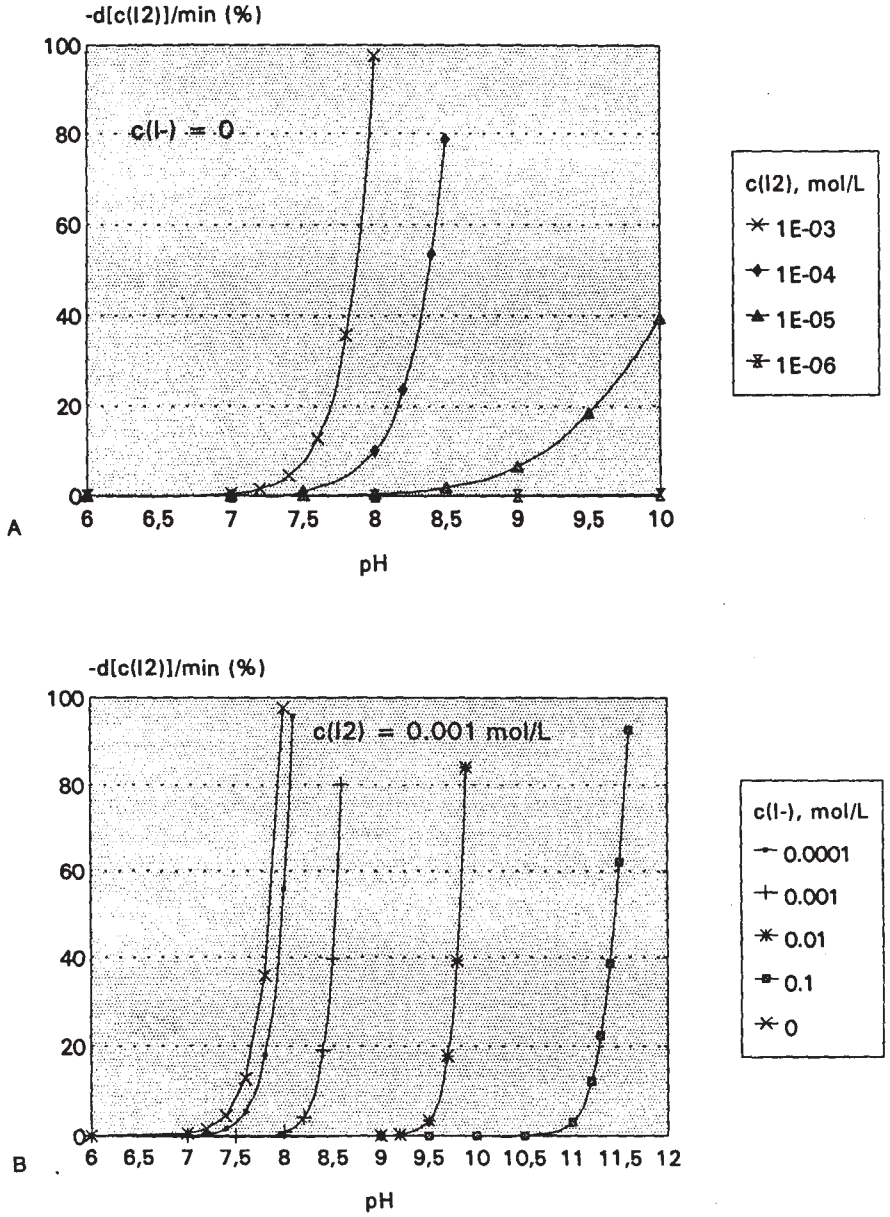

FIG. 8.4. Initial rates of iodate formation expressed as percentage loss of initial oxidation capacity. **A:** $c(I_2) = 10^{-3}$, 10^{-4}, 10^{-5}, 10^{-6} mol/L; no additional iodide. **B:** $c(I_2) = 10^{-3}$ mol/L; $c(I^-) = 0$, 10^{-4}, 10^{-3}, 10^{-2}, 10^{-1} mol/L. From these curves, it can be determined that, for example, in a 10^{-4} mol/L iodine solution at pH 8, the initial rate of loss of oxidation capacity is approximately 10% of the initial concentration per minute.

ever, even if possible, are of no use in a bactericidal context in a solvent that is itself a strong disinfectant.

Solutions of Iodophors

Iodophors are polymeric organic molecules (alcohols, amides, sugars) capable of complexing iodine species, resulting in reduced equilibrium concentrations of the species compared with those of pure aqueous solutions with the same total iodine and total iodide concentrations.

Because iodophoric preparations always contain appreciable iodide, the relevant species that must be considered are restricted to I^-, I_2, and I_3^-, for which the following (simplified) complexing reactions can be written:

$$I_2 + R \leftrightarrow R \cdot I_2 \ldots K_{I_2} \quad (11)$$

$$I_3^- + R \leftrightarrow R \cdot I_3^- \ldots K_{I_3} \quad (12)$$

$$I^- + R \leftrightarrow R \cdot I^- \ldots K_{I^-} \quad (13)$$

where R = structural regions of the iodophor molecule capable of forming complexes by steric or electronic effects.

To the extent that the chemistry of aqueous disinfectant solutions containing iodophors is understood, both electronic and steric effects are thought to be responsible for these interactions (Gottardi, 1985). Thus, taking as an analogy known interactions with oxygen compounds of low molecular weight, such as amides, esters, ketones, and ether (Yamada and Kozima, 1960; Schmulbach and Drago, 1960), it can be assumed that between molecular iodine and iodophor molecules, which without exception contain such functional oxygen-containing groups (e.g., povidone contains a carbonyl oxygen of the amide function in the pyrrolidinone ring), donor–acceptor complexes are formed [see also equation (11)], with iodine playing the part of the acceptor:

$$\rangle C{=}O + I_2 \rightarrow \rangle C{=}\overset{\delta+}{O} \ldots I - \overset{\delta+}{I}$$

Furthermore, the iodophors, especially in high concentrations, because of the spatial arrangement of the dissolved polymer molecules with near regions of helix-like structure (Horn and Ditter, 1984), clearly are able to surround the iodine species in the manner of clathrates and withdraw it from equilibrium [equations (11) through (13)]. This interaction must be important for the iodide ion and particularly for the large-mass triiodide ion, which cannot form a donor–acceptor complex because of their negative charge.

However, because no quantitative data (mass law constants) are available, an exact calculation for iodophoric preparations is not feasible. Nevertheless, qualitative investigations of the interactions with the iodophoric molecule polyvinylpyrrolidinone (Gottardi, unpublished data) reveal that K_{I^-} is much less than K_{I_2} and $K_{I_3^-}$. With regard to the normal conditions of use (i.e., presence of appreciable iodide and pH < 7), this has the following consequences (Gottardi, 1999):

1. HOI and the species derived from it (OI^-, HI_2O^-, I_2O^{2-}, and H_2OI^+) can be neglected.
2. Because the reactions in equations (11) through (13) reduce the equilibrium concentrations of I_2, I_3^-, and, to a certain degree, I^-, the species I_5^- and I_6^{2-} can be ignored as well.

Therefore, in iodophoric preparations, only the triiodide equilibrium [equation (3)] and the interactions of the iodophoric molecules with I_2, I_3^-, and I^- are important, all of which are independent of pH. Because HOI is virtually absent, stability problems concern only interactions with oxidizable components, but not disproportionation to iodate.

Influence of Temperature

Although not usually considered, temperature should not be overlooked. In a study dealing with ten different povidone–iodine preparations, the results for the relative alteration of free iodine with temperature fitted to an exponential function of the form

$$\Delta\%[I_2]_{\Delta t} = 100[10^{(0.023 \pm 0.0026)\Delta t} - 1$$

which is valid from 10° to 40°C (Gottardi and Koller, 1986). Following this equation, $[I_2]$ increases approximately 5.4% and 100% if the temperature rises 1.0° and 13.1°C, respectively. This increase of $[I_2]$ must be considered in the application of povidone–iodine preparations as disinfectants or antiseptics on living tissues. Because of their higher temperature (30° to 36°C), povidone–iodine preparations used on living tissues exhibit a significantly higher $[I_2]$ than they do at room temperature (Δt = 10° to 16°C; $\Delta\%[I_2]$ = 70% to 130%). Therefore, a significantly higher degerming efficiency can be expected compared with that obtained in vitro experiments, which usually are conducted at room temperature.

Atypical Behavior of Iodophors at Dilution

If 10% povidone–iodine is diluted, the concentration of free molecular iodine unexpectedly increases and passes through a maximum approximately in the 0.1% solution.

As can be seen in Fig. 8.5, the concentration of free iodine in a 10% povidone–iodine solution comes to approximately 2.0 mg and 8×10^{-6} mol/L and rises in a 1 : 100 dilution nearly tenfold. On further dilution, after passing the maximum ($[I_2] \approx 10^{-4}$ mol/L), the free iodine behaves increasingly "normally"—that is, it decreases—and below 0.01%, the povidone–iodine solution can be regarded as a simple aqueous solution of iodine.

Because $[I_2]$ depends not only on the concentration of povidone–iodine, but on total iodine (in general, 1%) and total iodide [iodine/iodide ratio; see Pinter et al. (1983)], and the presence of iodine-complexing pharmaceutical additives, it undergoes considerable variation. Figure 8.5 shows the typical course of $[I_2]$ of a pure aqueous povidone–iodine at dilution. The ordinate of the maximum (and to a lesser degree, its abscissa) therefore is not a constant for different iodophors and preparations containing iodophors. Figure 8.3 also shows the behavior of Lugol's solution on dilution, which explains the drastic reduction of free iodine caused by the complexing properties of the povidone molecules.

Individual Reactivities of Iodine Species

Much labor has been devoted to clear up these questions. Some answers are widely accepted:

Iodide (I^-), as a nonoxidizing species, has no degerming activity.

This is true for iodate (IO_3^-) as well, which acts as an oxidant only at an acid pH, as HIO_3 (pH < 4).

Free[1] iodine (I_2) is the only species with a proved correlation between equilibrium concentration and bactericidal activity. Its solvated forms, $I_2 \cdot H_2O$ or $I_2 \cdot ROH$ are thought to be the effective microbicidal agents in aqueous and alcoholic solution.

Triiodide (I_3^-) probably has no degerming activity, which was deduced from the negative effect that increasing the iodide concentration has on inactivation of polio virus (Krusé et al., 1970). On the other hand, triiodide represents the reservoir oxidation capacity in non-iodophoric preparations (Lugol's solution). It is the main species responsible for staining of tissue (Hickey et al., 1997).

Hypoiodous acid (HOI) is thought to contribute to bactericidal action, which is a plausible analogy with the system Cl_2/H_2O, where HOCl is the true active species.

Although Chang (1971) claimed differing behaviors of I_2 and HOI against certain germs, reports on the bactericidal properties of HOI and on attempts to establish a difference between I_2 and HOI should be treated cautiously (Gottardi, 1999). Although it is possible to manipulate an aqueous iodine solution to exhibit greater than 90% of its oxidation capacity as HOI (pH ≈ 8.5, no additional iodide), such systems in general have no practical importance, mainly because of stability problems. On the other hand, given a similar reactivity of I_2 and HOI in highly diluted systems [$c(I_2) \leq 10^{-5}$ mol] without additional iodide (as is usual in drinking water disinfection) and in the pH range of 3 to 9, a more-or-less constant bactericidal activity of iodine in aqueous solution can generally be expected (Gottardi, 1978a).

Iodine cation (H_2OI^+) is thought to be a very potent iodinating agent. Many publications identify this species as being responsible for disinfection, which can be traced back to a comprehensive and often-cited study dealing with the halogens in disinfection (Krusé et al., 1970). However, exact calculations (Gottardi, 1999) show that the iodine cation has some importance, if any, only under *very acidic* conditions (pH < 1) and in the *total absence* of additional iodide, where it amounts at the most to only approximately 0.3% of the total iodine at high dilutions (Fig. 8.2D). Under conditions used in practice (i.e., in the presence of iodide to regulate the concentration of free molecular iodine and improve stability), however, *the iodine cation is virtually absent* and therefore of no importance. For example, a solution with $c(I_2) = 0.001$ and $c(I^-) = 0.01$ mol/L generates $[I_2] = 1.31 \times 10^{-4}$ mol/L or 33.3 ppm at pH < 8 (Fig. 8.3C). The concentration of the iodine cation, however, comes to $[H_2OI^+] = 2.15 \times 10^{-13}$ mol/L (not shown in Fig. 8.3C), which is approximately *nine orders of magnitude* less than $[I_2]$. Even if we attribute a higher reactivity to the iodine cation, which is thought to play an important role in certain substitutions, this can hardly explain any real contribution to the disinfecting process.

[1]The term *free* serves to distinguish this I_2 from complex-bound I_2, as discussed later for iodophoric preparations, and refers to the solvated forms $I_2 \cdot H_2O$ and $I_2 \cdot ROH$.

Virtual Impossibility of Discriminating Microbicidal Activities of I_2 and HOI

A frequently quoted issue is the contribution of free molecular iodine, I_2, and hypoiodous acid, HOI, to disinfection processes and the differences in their bactericidal power (Krusé, 1970). As set forth previously, a solution containing predominantly I_2 needs a pH of less than 5 and absence of iodide, whereas a solution containing predominantly HOI needs a pH of approximately 8.4. A comparison of the killing effect of I_2 and HOI presupposes that the susceptibility of bacteria for interaction with these iodine species is the same in both pH ranges, which is a coarse simplification. Therefore, a definite differentiation of both species probably is not feasible, an assertion that applies also to other iodine species as well.

Stability of Iodine-based Disinfectants

Iodine and other disinfectants based on halogens in the oxidation states 0 or +1, as long as they are not present as pure substances (i.e., without a solvent), can gradually lose part of their degerming properties (e.g., during storage). This is due to (a) substitutions of covalent hydrogen (e.g., O-H, N-H, C-H, as a result of reactions with solvent molecules and pharmaceutical additives); (b) additions to olefinic double bonds; and (c) the disproportionation of hypohalous acid to halate in aqueous preparations [equation (9)], which has no degerming properties (see earlier). Although substitutions, which in the case of iodine are thought to be fewer than with chlorine and bromine, and additions can be avoided by an appropriate composition, the equilibria in equations (1) through (8) are established in any case if water is present, and iodate formation [equation (9)] can begin.

On the basis of calculated equilibrium concentrations, reaction times, and initial rates of iodate formation, the following conclusions have been drawn concerning the stability of iodine-containing disinfecting solutions (Gottardi, 1978a, 1981, 1999):

1. Below pH 6, a decrease in disinfection efficacy because of the formation of iodate can be excluded.
2. Above pH 7, the formation of iodate, the extent of which largely depends on the pH value as well as on the iodide concentration, must be regarded carefully.

Raising the pH value lowers the stability (iodate formation increases), whereas raising the iodide concentration improves the stability (iodate formation is reduced).

3. Because of the stabilizing effect of the iodide ion, provided that its concentration is high enough, the opposing effect of the pH value can be overcompensated. As a result, iodine-based preparations can also exhibit sufficient stability for practice in the weak alkaline range (e.g., Lugol's solution, at pH < 9).
4. In highly diluted iodine solutions ($<10^{-5}$ mol/L, or 2.54 mg/L), which are used to disinfect potable water or swimming pool water, only a slow iodate formation can be expected even in absence of additional iodide and pH 8 or lower. In accordance with this, in iodine-based disinfection plants, no significant amounts of iodate have been detected (Black et al., 1968).

The Absence of N-*iodo Compounds in Aqueous Solution*

The well known equilibria of halogen with N-H compounds:

$$X_2 + \rangle N - H \leftrightarrow \rangle N - X + H^+ + X^- \quad (14a)$$

$$HOX + \rangle N - H \leftrightarrow \rangle N - X + H_2O \quad (14b)$$

leads to numerous *N*-chloro compounds that play an important role in chlorine-based disinfection practice; this, however, is not the case with iodine.[2] Although *N*-iodo compounds can be synthesized in a nonaqueous system (Gottardi, 1974, 1975), in contact with water they immediately hydrolyze:

$$\rangle N - I + H_2O \rightarrow \rangle N - H + HOI \quad (15)$$

HOI immediately begins to disproportionate according to equation (9); iodide and protons develop, and a comproportionation reaction [reverse of reaction equation (1)] also takes place, forming molecular iodine. Within minutes, the reaction settles, and the ratio of resulting products, I_2 and IO_3^-, complies with the stoichiometry set forth in equation (16) (Gottardi, 1978b):

$$5 \rangle N - I + 3H_2O \rightarrow 5 \rangle N - H + 2I_2 + H^+ + IO_3^- \quad (16)$$

Because the equilibria of equations (15) and (16) are lying far on the right side practically no *N*-iodo compound is present and the reverse reactions of eq 14a, b do not take place. *N*-iodo compounds, therefore, are virtually without any relevance for disinfection.

[2]This assertion complies with the pH range relevant for disinfection (pH 4 to 8) and not with alkaline conditions at 0°C, where *N*-iodo alkylamines can be synthesized even in aqueous solutions (Jander et al., 1972).

Reaction with Proteinaceous Material: Bacterial Kill and Consumption Effects

Halogens react not only with living microorganisms but with dead ones and with dissolved proteins. In contrast to chlorine, where oxidizing (and bactericidal) *N*-chloro compounds still emerge, with of iodine these reactions (consumption effects) are associated only with a loss of oxidation capacity [equations (16) to (18)] because *N*-iodo compounds are not formed (see earlier).

Interaction with thiols (S-H compounds) runs in two directions, with oxidation to disulfides [equation (16a)] on the one hand, and to sulfur-oxygen acids [i.e., sulfenic, sulfinic, and sulfonic acids; equation (16b)], on the other hand. Because these reactions run with similar speed, the proportions of the diverse products are mainly governed by the mode of mixing. Equation (17) describes substitution at activated aromatic compounds (e.g., the amino acids tyrosine, histidine, and the nucleosides cytosine and uracil), whereas equation (18) refers to the addition of I_2 to the olefinic function of unsaturated fatty acids:

$$R - SH \xrightarrow[-2H^+,2I^-]{+I_2,+R-SH} R - SS - R \quad (16a)$$

$$R - SH \xrightarrow[-2H^+,2I^-]{+I_2,\ H_2O} R - SOH \xrightarrow[-2H^+,2I^-]{+I_2,\ H_2O} R - SO_2H \xrightarrow[-2H^+,2I^-]{+I_2,\ H_2O} R - SO_3H \quad (16b)$$

$$= CH - + I_2 \rightarrow = CI - + H^+ + I^- \quad (17)$$

$$- CH = CH - + I_2 \rightarrow - CIH - CHI - \quad (18)$$

Iodine's Mode of Action as a Microbicide

Iodine, mainly in its molecular form, can penetrate the cell wall of microorganisms rapidly (Chang, 1971), which can be deemed its fundamental feature. Although exact details about the killing of a living cell by the I_2 molecule (or one of the reaction products occurring in aqueous solution) are not known, it is plausible that microbial kill by iodine is based on the reactions outlined in equations (16) through (18), which could have the following consequences:

1. Oxidation of the SH group (Krusé et al., 1970) of the amino acid cysteine results in loss of the ability to connect protein chains by disulfide (—S—S—) bridges, an important factor in the synthesis of proteins.
2. Iodination of the phenolic and imidazolic groups of the amino acids tyrosine and histidine, which easily form monoiodo or diiodo derivatives, and iodination of the pyrimidine derivatives cytosine and uracil could increase the bulk of the molecules, leading to a form of steric hindrance in hydrogen bonds. As was postulated for the interaction with hypochlorous acid

(Prütz, 1996), this could cause denaturation of DNA through dissociation of the double strand into single strands. Because of the bulk of the large iodine atoms, this effect should be even more pronounced in case of an iodine-based disinfectant.

3. The addition of iodine to unsaturated fatty acids [equation (18)] is thought to lead to a change in the physical properties of the lipids and to cause membrane immobilization (Apostolov, 1980). Electron microscopy and biochemical observations support the conclusion that iodine, by interacting with the double bonds of phospholipids causes damage of the cell wall which leads to a loss of intracellular material (Reimer et al., 1998).

Of the preceding points, the first might be the most important, both because of the ubiquitous SH groups and the very fast and irreversible reaction with iodine.

Effect of Iodine-consuming (Reducing) Material

In in vitro experiments using peptone solutions, it was shown that iodine reacts with proteins at least three times slower than chlorine and nearly four times slower than bromine (Gottardi, 1976). Hence, in disinfection under conditions occurring in practice, that is, in the presence of dissolved proteins (blood, serum, sputum), iodine is much more efficient than chlorine (and bromine) because the share of the halogen concentration available for the actual degerming reaction is considerably greater. The comparatively low reactivity with proteins (no *N*-iodo compounds), which is sufficient, however, to achieve high killing rates, is one of the reasons for the excellent degerming properties of iodine.

However, there is a minor drawback with iodine that is not relevant for chlorine disinfection. As can be deduced from equations (16) through (18), consumption effects are always connected with the formation of iodide [which is the only iodine-derived reaction product in equation (16a, b)]. Thus, according to the reactions in equation (16) through (18), not only is the reservoir of available iodine (oxidation capacity) diminished, but the triiodide equilibrium [equation (3)] is shifted to the right. This means that the bactericidal power (which is a function of $[I_2]$) is diminished to a higher degree than would be estimated on the basis of the loss of total iodine. This disadvantage is avoided with formulations that can reoxidize the formed iodide, such as "enzyme-based iodine" (Duan et al., 1999; Hickey et al., 1997).

PREPARATIONS CONTAINING OR RELEASING FREE IODINE

Solutions of Iodine and Iodide

To this group belongs a great variety of preparations containing elemental iodine and potassium (or sodium) iodide in water, ethyl alcohol, and glycerol, or in mixtures of these solvents. They rank with the oldest disinfectants and have survived more than 150 years owing to their efficacy, economy, and stability. The following are the official preparations according to the *United States Pharmacopeia XXIII* (USP XXIII): (a) Iodine Topical Solution, an aqueous solution containing 2.0% iodine and 2.4% sodium iodide; (b) Strong Iodine Solution (Lugol's Solution), an aqueous solution containing 5% iodine and 10% potassium iodide; (c) Iodine Tincture, containing 2.0% iodine and 2.4% sodium iodide in aqueous ethanol (1 : 1); and (d) Strong Iodine Tincture, containing 7% iodine and 5% potassium iodide in 95% ethanol. Because all of these preparations contain large amounts of iodide (0.16 to 0.6 mol/L), only the triiodide equilibrium [equation (3)] becomes important. As a result, these solutions virtually contain only molecular iodine, iodide, and triiodide and are therefore very stable because there is no HOI present (see earlier). Because of their high content of free molecular iodine (e.g., Lugol's solution $[I_2]$ = 155.6 ppm), they are powerful disinfectants with the disadvantage of staining and a toxic potential that should not be underestimated (see Toxicity).

Preparations Containing Organic Complexing Agents

In addition to preparations with complexing agents of low molecular weight, such as tetraglycine hydroperiodide (Gershenfeld, 1977) or the inclusion compound iodine-maltosylcyclodextrin (Kawakami et al., 1988), this group includes the important *iodophors,* a term indicating in general the combination of iodine with a carrier (as these complexing agents usually are called) of high molecular weight. In aqueous solution, iodophors form the same iodine species as do the pure aqueous iodine solutions (see earlier). However, the polymer carriers, because of their complexing properties, partly reduce the equilibrium concentrations of the iodine species and give the iodophor preparations properties that make them superior in some respects to solutions containing only iodine and iodide.

Iodophors

An iodophor is a complex of iodine with a carrier that has at least three functions: (a) to increase the solubility of iodine, (b) to provide a sustained-release reservoir of the halogen, and (c) to reduce the equilibrium concentration of free molecular iodine. The carriers are neutral polymers, such as polyvinylpyrrolidinone, nonylphenoxy polyethoxyethanol, polyether glycols, polyvinyl alcohols, polyacrylic acid, polyamides, polyoxyalkylenes, and polysaccharides.

In the solid state, iodophors form deep brown to black, crystalline powders that usually do not smell of iodine,

indicating a tight bonding with the carrier molecules. Their solubility in water is good but depends on the chain length of the polymeric molecules and varies in the case of povidone–iodine between 5% (type 90/04, average molecular weight near 1,000,000) and more than 20% (type 17/12, average molecular weight near 10,000). The best known iodophor is povidone–iodine, a compound of 1-vinyl-2-pyrrolidinone polymer with iodine, which according to USP XXIII contains not less than 9.0% and not more than 12.0% available iodine. On the basis of spectroscopic investigations (Schenck et al., 1979), it was found that povidone–iodine (in the solid state) is an adduct not with molecular iodine (I_2) but with hydrotriiodic acid (HI_3), where the proton is fixed by a short hydrogen bond between two carbonyl groups of two pyrrolidinone rings and the triiodide anion is bound ionically to this cation (Fig. 8.6).

A completely different situation occurs in solution, where this structure no longer exists and equilibria between I_2, I^-, I_3^-, and the polymeric organic molecules are established [equations (3) and 11 through (13)]. The high concentration of carrier molecules (approximately 90 g/L) results in the content of free molecular iodine being greatly reduced in such preparations (10% aqueous solution of povidone–iodine: $c(I_2) \approx c(I^-) \approx 0.04$ mol/L, $[I_2] \approx 1 \times 10^{-5}$ mol/L or 2.54 ppm) compared with pure aqueous solutions with the same total iodine and total iodide content (aqueous iodine solution: $c(I_2) = c(I^-) = 0.04$ mol/L, pH 5: $[I_2] = 5.77 \times 10^{-3}$ mol/L or 1,466 ppm.[3] The high content of free iodide (which varies between 10^{-3} and 10^{-1} mol/L, according to the preparation) also means that HOI can be disregarded, and only I_2 is responsible for disinfection (see earlier).

Relevance of Free Molecular Iodine to the Efficiency of Iodophor Preparations

The real bactericidal agent is free molecular iodine, because it is this species alone for which a correlation between concentration and bactericidal activity has been proved, and not for the total iodine or iodophor concentration (Berkelmann et al., 1982; Pinter et al., 1983; Gottardi and Puritscher, 1986; Hickey et al., 1997).

However, the various commercial preparations differ in the amount and kind of pharmaceutical additives, such as detergents and back-fatting agents, all of which usually have iodine-complexing properties, as well as in the ratio of total iodine to total iodide (Pinter et al., 1983). This results in a significant difference in the concentration of free molecular iodine in spite of the fact that the actual iodophor concentration or the concentration of the total (titratable) iodine might be the same.

[3]This is a hypothetical value because the solubility of molecular iodine lies at 334 ppm (25°C), and an aqueous solution of this composition contains undissolved iodine.

These circumstances make it necessary to determine the free iodine, which can be measured by three different methods: (a) by extraction with a nonpolar solvent, such as heptane (Pollack and Iny, 1985); (b) by dialysis (Horn and Ditter, 1984); and (c) by a potentiometric method (Gottardi, 1983). Free iodine is the yardstick for bactericidal potency (killing rate), whereas the total iodine, which follows from the specification or simply can be assayed by titration, points to the disinfection capacity. The latter comprises *all* oxidizing iodine species and therefore should not be confused with the free molecular iodine, which (except in highly diluted solutions; see Fig. 8.5) amounts to only a small fraction of the total available iodine. For aqueous preparations, determination of free iodine is a reliable and simple means to predict bactericidal properties (Gottardi and Puritscher, 1986) and, as already pointed out, should be specified by the manufacturer.

However, because the aforementioned methods for analyzing free iodine are established for aqueous systems, measurements in alcoholic solutions or water/alcohol mixtures not only need special calibrations, but do not give true correlations with the bactericidal potential because the solvent is itself bactericidal. Another restraint is that some pharmaceutical ingredients (e.g., detergents) in commercially available iodophor preparations may influence the susceptibility of a living microorganism to iodine and disturb the correlation between bactericidal activity and concentration of free iodine.

Forms of Application

According to USP XXIII, the following application forms of povidone–iodine are approved: Povidone–Iodine Topical Solution, Povidone–Iodine Cleansing Solution, Povidone–Iodine Ointment, and Povidone–Iodine Topical Aerosol Solution. With regard to available iodine, all must contain not less than 85% and not more than 120% of the labeled amount. In general, povidone–iodine preparations contain 1% to 10% povidone–iodine, which is equivalent to 0.1% to 1.0% available iodine. They may contain a small amount of alcohol (Topical and Cleansing Solution); the cleansing solutions contain one or more surface-active agents. The aerosol solution, however, is a povidone–iodine solution under nitrogen in a pressurized container.

Influence of Iodine Consumption on the Efficacy of Povidone–Iodine Preparations

Because iodophoric preparations are mainly used as medical antiseptics, the influence of iodine-consuming body fluids is a very important feature with regard to bactericidal capacity and rate. Mainly in presence of blood, which is characterized by numerous SH functions, the reservoir of available iodine is substantially diminished and, because of the formed iodide, the triiodide equilibrium [equation (3)] is shifted to the right. Both

effects decrease the proportion of free molecular iodine (see earlier).

On the other hand, when povidone–iodine preparations are contaminated with liquid substrata, the dilution effect (see earlier) causes an increase in the equilibrium concentration of free molecular iodine (Fig. 8.5). The extent to which this effect compensates for the other two depends on the content of reducing substances. Thus, with whole blood, a large decrease in the concentration of free molecular iodine occurs, whereas in the presence of plasma (exudates), the concentration remains unchanged if the ratio blood to povidone–iodine is not too high (Gottardi and Koller, 1987).

Quantitative investigations into the consumption of iodine (and other oxidizing substances) with blood are distinguished by poor reproducibility, which can be attributed to the different reactions of iodine with SH groups [equation (16a, b)]. In practice, no substantial decrease in the bactericidal efficacy of 10% povidone–iodine preparations is likely with body fluids having a composition similar to plasma (volume substrate/volume 10% povidone–iodine ≤ 0.6). However, contamination by 25% or more whole blood should be avoided.

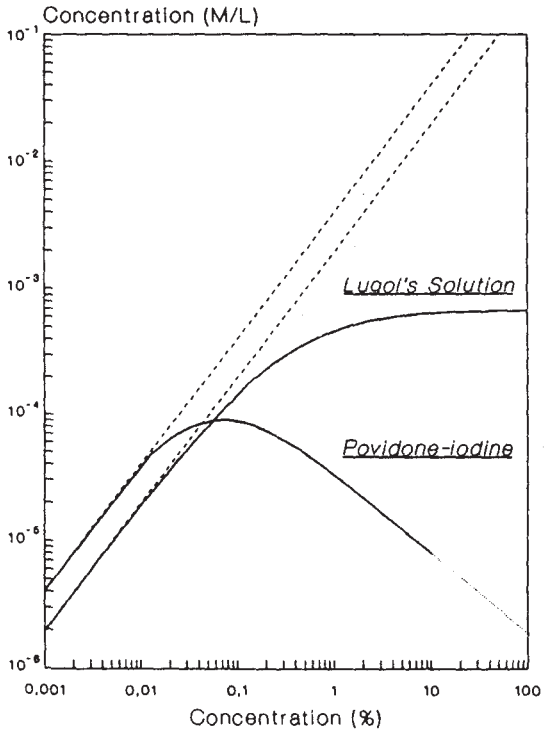

FIG. 8.5. Total available *(dashed lines)* and free molecular *(solid lines)* iodine in aqueous povidone–iodine (determined potentiometrically) (Gottardi, 1983) and in Lugol's solution [calculated after Gottardi (1980)].

Iodophoric Preparations and "Active Agents"

In the search for the ideal disinfectant (i.e., the impossible combination of immediate bacterial kill with complete lack of unwanted side reactions), much work was done by microbiologists comparing preparations based on different chemistries or killing mechanism (e.g., chlorine, iodine, aldehydes, peroxides, chlorhexidine, quats).

The results of such studies usually are presented in such terms as, for example, " . . . 0.25% chlorhexidine and 0.025% benzalkonium chloride was more (or less) effective than 10% povidone iodine . . .." Such a formulation implies that povidone–iodine is an active agent; however, this is not the case. The basic requirement to designate a substance as an active agent are (a) a defined molecule and, (b) a positive correlation between the concentration of these defined molecules and bactericidal activity. Both criteria are not fulfilled with povidone–iodine.

With regard to the nature of povidone–iodine and its disinfecting properties, the following points have been made (Gottardi, 1991):

1. Although povidone–iodine in the solid state forms a crystalline powder with a delineated structure in which iodine is present in form of discrete HI_3 units (Fig. 8.6), it is not a uniform compound because the polymeric carrier molecules show a molecular weight distribution. In aqueous solution, however, there no longer are HI_3 molecules but an equilibrium between I^-, I_2, and I_3^-, which are more or less complexed with the organic carrier molecules.
2. Povidone–iodine preparations with 10% povidone–iodine and 1% titratable iodine can easily be adjusted to contain a range of 0.1 to more than 20 ppm free molecular iodine (I_2). Indeed, in a comparison of ten commercially available preparations, a range of 0.2 to 10 ppm free molecular iodine was found (Gottardi and Koller, 1986a).
3. Because of a possible range in $[I_2]$ of approximately two orders of magnitude, preparations specified to contain 10% povidone–iodine will probably exhibit remarkable variations in bactericidal activity.
4. Because there is no direct and positive correlation between bactericidal activity and the concentration

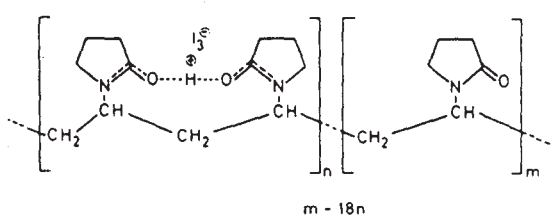

FIG. 8.6. Structure of solid povidone–iodine (Schenck et al., 1979).

of povidone–iodine (dose–action relation), it follows that povidone–iodine cannot be regarded as an *active agent* (like chlorohexidine), but rather as a *pharmaceutic base material.*

5. As long as free molecular iodine (the most important species) is not specified, both quantitative killing results (log reductions) and evaluation of toxicity relate only to the *batch number X* of the *preparation Y* of the *manufacturer Z,* and do not contribute to solution of basic issues of iodine and disinfection.
6. Results of comparisons of povidone–iodine with preparations with specified active agents (e.g., 70% alcohol, 0.2% octenidine, 0.5% chlorhexidine) should not be generalized because they are misleading.

Although they have been published (Gottardi, 1991), these assertions are not accepted (obviously because they are not read or understood); this also applies to the previously stated necessity to specify for iodine-based preparations, in addition to total (titratable) iodine, at least the free molecular iodine, which provides information about toxic effects as well as microbicidal activity. It is a serious sin of omission on the part of official institutions not to insist on specification of free molecular iodine in iodine-based preparations.

Solid Iodine-based Microbicidal Compositions

To this group belong resins containing quaternary ammonium groups loaded with triiodide and higher polyiodide ions (e.g., pentaiodide). In contrast to the "classic" disinfectants, which contain antimicrobial agents that are dispersed in a liquid (or gas) phase, these resins rank among the "nonclassic chemical disinfectants," which consist of active moieties attached to, associated with, or stored in (or a combination thereof) a solid phase (Kril et al., 1986). Their mode of action is explained either by direct, physical contact with their surface or by slow release of a disinfecting agent (in this case, iodine) into the bulk phase being disinfected. Because the residuals of total iodine washed out by the water flowing through the resin are very low, the resins seem to be ideally suited for application in point-of-use water purification units (Osterhoudt (1997).

Preparations Producing Iodine In Situ

Preparations of this kind do not contain elemental iodine, but rather iodide (NaI or KI), and produce the former by an oxidation process ($2I^- \rightarrow I_2 + 2e^-$) that can be performed either chemically or by electrical current. In the first (chemical) case, we are dealing in general with stable, dry powder concentrates that start to produce iodine only when they come in contact with water. Examples of oxidants that were used to produce iodine in situ are chloramine-T, 1,3-dichloro-5,5-dimethylhydantoin (White, 1972), and NH_2Cl (Kinman, 1976). A more recent development uses calcium peroxide as an oxidant and horseradish peroxidase as a catalyst (Hickey et al., 1997). The great advantage of this concept, called *enzyme-based iodine* (EBI), lies in the combination of a relatively high concentration of free molecular iodine (15 ppm) with a comparatively very low concentration of total iodine (≈30 ppm). This is in contrast to, for example, iodophoric preparations, where the ratio is not 1 : 2 but approximately 1 : 1,000. In addition, the EBI system is able to reoxidize reduced iodine, which results in a constant level of active iodine during its use-life. This outstanding feature was demonstrated in repeated cycles of endoscope processing (Duan et al., 1999).

The production of iodine by anodic oxidation of an aqueous iodide solution is another possibility for supplying a diluted disinfecting solution in situ in the large volumes recommended for municipal drinking water supplies, cooling towers, and swimming pools (Sampson and Sampson, 1995). In a closed disinfecting system, electric current can be used to reoxidize consumed (reduced) iodine, for which potentiometric steering is possible (Gottardi, unpublished data).

Synopsis of Composition and Active Iodine Forms in Disinfectant Solutions

Table 8.1 gives a synopsis of the different preparations containing iodine and the applications for using iodine. Besides the total concentration of iodine and iodide, the presumable active species and their calculated, measured, or estimated equilibrium concentrations are shown. Furthermore, a tentative description of the conditions in alcoholic solutions is given. In contrast to pure alcoholic solutions (containing only iodine and an alcohol), where iodine predominantly occurs in the solvated molecular form, $I_2 \cdot ROH$ (besides some triiodide; see Alcoholic Solution), alcoholic preparations used in practice (Tincture and Strong Tincture of Iodine, USP XXIII) also contain iodide and water, with the result that the equilibria in equations (1) through (8) also are established. However, because of the iodide content, no HOI is present, and only the solvated iodine molecules $I_2 \cdot ROH$ and $I_2 \cdot H_2O$—apart from the alcohol itself—appear to be responsible for disinfection. A differentiation between the two forms with regard to relative reactivity should favor the hydrate complex because of the greater stability of the I_2–alcohol–solvate complex (the inductive effect of the alkyl group increases the electron-donating properties of the oxygen).

HOI as a virtual contributor to the microbicidal process may be expected only in iodine/water systems of high dilution and very low iodide concentration, as is the case with iodine disinfection of drinking and swimming pool water.

TABLE 8.1. *Composition and active iodine form in disinfectant solutions containing iodine*

Components	Solvent	Examples	Total iodine content (total iodide content)	Iodine form mainly responsible for microbicidal effect (concentration proportion of the total iodine concentration)
I_2	Ethanol	Solution of iodine in alcohol	1%	I_2·ROH
	H_2O	Drinking water, swimming pool iodination	10^{-5}–10^{-6} M/L	I_2·aq, HOI ([I_2] + [HOI]: 0.25–2.5 ppm[a]; 98%–100%)
I_2, I^-	H_2O	Lugol's solution	5% (10% KI)	I_2·aq (155.6 ppm[a]; 0.31%)
I_2, I^-	H_2O	Enzyme-based iodine 30–40 ppm (110–130 ppm)		I_2·aq (15 ppm; ~50%)
	Ethanol/H_2O	Iodine tincture	2% (2.4% NaI)	I_2·ROH, I_2·aq
I_2, I^-, polym. org. complexing agents,[c] additives[d]	H_2O	Mucosal disinfectant and washing concentrates based on iodophores	0.5%–1.0% (iodide content varies greatly depending on the preparation)	I_2·aq (0.2–10 ppm[b]; 0.003–0.1%)
	Propanol/H_2O	Skin disinfectants (sprays)	0.1% (0.05%)	I_2·ROH, I_2·aq

[a]Calculated (see Gottardi, 1999).
[b]Measured potentiometrically (see Gottardi, 1983) in commercially available products.
[c]Povidone, polyoxyalkylenes, polyetherglycols, and the like.
[d]Buffers, detergents, foam stabilizers, artificial colourings, and the like.

TABLE 8.2. *Practical applications of iodine as a disinfectant: concentration, exposure time, disinfective result*

Scope of application	Concentration	Conditions	Exposure time	Disinfective result	References
Drinking water	8 ppm	—	10 min	"Kill of water-borne pathogens"	Committee on Medical Research (1948)
	3–4 ppm	25°C	12 min	"Reduces 10° bacterial/mL to less than 10 bacterial/mL"	Chang and Morris (1952)
	3–4 ppm	3°C	22 min		
Drinking water in emergency	5–6 ppm	20°–25°C	10 min	"Excellent disinfectant for water supplies under emergency conditions"	
	5–6 ppm	near 0°C	20 min		
	5 drops I_2 tincture to a quart of water	Clear water	30 min	"Water safe for drinking"	United States Public Health Service (1940)
	10 drops I_2 tincture to a quart of water	Cloudy water	30 min		
	4.0–8.0 mg/L	Turbid water of low quality	30 min	"Water of virtual potable quality"	Ellis and van Voce (1989)
Swimming-pool water	0.2 (0.1) ppm	—		"Provides water of satisfactory quality"	Black et al. (1959)
	0.2 ppm	—		"Maintains the water at a satisfactory bacteriological quality"	U.S. Public Health Service (1962)
General germicidal action	1:20,000	Absence of organic matter	1 min	"Most bacteria are killed"	Goodman and Gilman (1980)
	1:20,000	Absence of organic matter	15 min	"Wet spores are killed"	Goodman and Gilman (1980)
	1:200,000	Absence of organic matter	15 min	"Will destroy all vegetative forms of bacteria"	Goodman and Gilman (1980)
Disinfection of skin	1% tincture	—	90 s	"Will kill 90% of the bacteria"	Goodman and Gilman (1980)
	5% tincture	—	60 s	"Will kill 90% of the bacteria"	Goodman and Gilman (1980)
	7% tincture	—	15 s	"Will kill 90% of the bacteria"	Goodman and Gilman (1980)
	1% aqueous I_2 solution	Skin of hands	20 min	"Inactivation of rhenovirus"	Carter et al. (1980)
	2% aqueous I_2 solution	Skin of hands	3 min	"Inactivation of rhenovirus"	Carter et al. (1980)

ORGANIC IODINE COMPOUNDS

Compounds of this class contain iodine bound to a carbon atom, and they differ from the previously described disinfectants in that they contain no free iodine and are not oxidizing. Iodoform (triiodomethane), probably the oldest pharmaceutically used iodine compound, forms yellow crystals with a characteristic anesthetic odor. It came into extensive use as a dusting powder, especially as a local antiinfective agent to promote granulation and diminish infections of open wounds (Gershenfeld, 1977). Because of its toxicity (it may cause sleeplessness, hallucinations, and spasms), it has been replaced by other preparations, especially those containing iodophors, and it is no longer specified in the USP.

A special application still in use is the filling of cavities in dentistry and oral surgery with triiodomethane-containing pastes or triiodomethane-coated gauzes. Particularly, a calcium hydroxide–iodoform mixture was favored as a root filling material (Kubota et al., 1992). Filling of large cavities, however, should be avoided because O'Connor et al. (1977) reported on a severe iodoform toxicity with bismuth–iodoform–paraffin paste gauze after a total maxillectomy. With regard to its bactericidal mechanism, iodoform was thought to produce elemental iodine and formaldehyde in connection with water (Knolle, 1975). This assertion seems doubtful because it was impossible to detect any free iodine in an aqueous slurry of CHI_3 at 37°C and pH 7 with a method that is sensitive down to 2.5×10^{-8} mol/L (Gottardi, 1982).

Iodine derivatives of quinoline exhibit protozoicidal and metazoicidal properties and have shown excellent results in prophylactic and therapeutic use (Gershenfeld, 1977). Iodoquinol (USP XXIII, 5,7-diiodo-8-quinolinol) and clioquinol (USP XXIII, 5-chloro-7-iodo-8-quinolinol) are the best known active substances of this type and serve as the basis for creams, ointments, powders, and tablets. To this class of compounds also belong the iodine-containing x-ray contrast media. Examples are iocetamic acid, iopanoic acid, and iothalamic acid (all USP XXIII). They contain a benzene ring system with three iodine atoms in meta-position, and are used as such but also in the form of their derivatives. The radioactive compounds iodohippurate sodium I 123 and I 131 (USP XXIII) are used for nuclear medical purposes. Of only historical interest are the iodonium compounds, with the general formula $[R_2I^+]X^-$, where R is an organic radical and X^- an inorganic or organic anion (e.g., diphenyliodonium chloride). The structure resembles that of the onium compounds (e.g., quaternary ammonium), and the active part of these compounds is iodine in the oxidation state +3 (Gershenfeld and Witlin, 1948).

TOXICITY

Toxicity comprises all unwanted side reactions that can be classified as primary effects, like *irritation* and *staining*, and secondary effects that are the biologic consequences of *incorporation*. In discussing these features, it is necessary to take into account (a) the composition of the preparation, that is, the equilibrium concentrations of the iodine species I_2, I^-, and I_3^-; (b) their specific contribution to toxic effects; (c) the nature of the tissue coming in contact with the iodine system; and (d) the mode and time of application.

Irritation is a result of iodinating or oxidizing reactions for which free molecular iodine is chiefly responsible. Because these reactions are the same as those that cause bacterial kill, in general a positive correlation between both features can be expected. However, the surprisingly low toxicity of the low-level EBI disinfecting system (Duan et al., 1999) reveals that a high concentration of free molecular iodine (15 ppm) is well tolerated if total iodine (triiodide) is very low (30 to 40 ppm).

Staining is mainly caused by the triiodide ion and only to a minor degree by free molecular iodine (Hickey et al., 1997). The deep brownish color on skin is often misinterpreted as a kind of burn.

For *incorporation* effects, two routes are possible: diffusion through the treated tissue, and uptake as drinking water. In the first case, uncharged molecular iodine plays the main role because it is able to diffuse through the skin. For the ionic species like I^- and I_3^-, however, intact skin acts as a barrier (Goldsmith, 1983). The triiodide ion, therefore, is retained in the outer, horny layers of the skin, where it causes staining that cannot be removed by washing. However, because of the equilibrium $I_3^- \leftrightarrow I_2 + I^-$, as long as staining is visible, molecular iodine is formed and diffuses into deeper regions of the skin, where its reduction causes an increase in serum iodide. On the other hand, there is also diffusion out of the skin, causing a remanent bactericidal action (see later). Therefore, staining, although caused by the charged species I_3^-, also leads to real incorporation, and should be seen as a sign of toxicity. The contribution of iodide to incorporation is confined to ingestion (iodinated drinking water, iodide-containing foodstuffs) and resorption with disinfection of mucous membranes.

Although the symptoms are clear in irritation and staining, the secondary effects (based on incorporation) have diverse manifestations: elevated iodide levels in urine and serum, and deviations (usually an increase) in serum levels of parameters connected with thyroid function, T_4 (thyroxine or tetraiodothyronine), T_3 (triiodothyronine), and thyrotropin (thyroid-stimulating hormone; TSH).

Topical Antiseptic Preparations

Iodine Tincture

High doses of free iodine, such as in form of iodine tincture, are highly toxic if brought into body cavities, and cause swelling and bleeding of mucous membranes.

Consumption of 30 g of iodine tincture can be fatal (Wirth et al., 1967). As an antidote for such accidents, 10 to 20 g sodium thiosulfate (reduction of iodine to iodide) or starch (formation of inclusion compounds) orally is recommended (Kuschinsky and Lúllmann, 1984).

Lugol's Solution

The high concentration of free iodine ($[I_2]$ = 155.6 ppm) in Lugol's solution makes it a powerful disinfecting but also rather toxic solution, with strong staining properties grounded in the high triiodide concentration (0.18 mol/L). It should be used only externally on very small areas, where it can be recommended in emergencies (e.g., at injuries by contaminated hypodermic needles).

Enzyme-based Iodine

Toxicity tests, including oral toxicity, primary dermal irritation, acute inhalation, ocular toxicity, acute dermal irritation, and sensitization assays in test animals (rat, rabbit and guinea pig), showed that except for slight irritation to the unwashed rabbit eye and in the primary dermal test, there was no evidence of toxicity for EBI (Duan et al., 1999). The authors attribute this low toxicity for external and internal surfaces of animals to the low level of total iodine (i.e., triiodide) in the germicide.

Povidone–Iodine

Povidone–iodine preparations were introduced in the 1960s with the aim of preventing primary toxic effects, based on their low concentration of free molecular iodine. Their low toxic potential was inferred from the increase in serum iodide with their use, which is less than with iodine tincture or Lugol's solution (Knolle, 1975). Because the carrier polyvinylpyrrolidinone was used as a blood substitute, toxicity can be considered a secondary problem. The good tolerance to povidone–iodine is apparent in its successful application in healing burned skin, although iodine resorption remains a drawback. Hunt et al. (1980) found that the amount of absorbed iodine was directly related to the size of the burn. Kuhn et al. (1987) also state that on treating burns with a povidone–iodine preparation, plasma iodine (i.e., iodide) sharply increased from 6.4 ± 0.4 to 20.7 ± 4.7 μg/100 mL; however, the authors also state that thyroid function does not seem to be modified by plasma iodine overload. Glöbel et al. (1984) investigated iodine uptake after use of povidone–iodine preparations (Betaisodona) as oral antiseptic, vaginal gel, and liquid soap in subjects with normal thyroid function. By measuring serum iodide, T_3, T_4, and TSH and the urinary iodide excretion (as an index of thyroid function), the authors observed an increase in the iodine supply of up to 2 mg daily, but in no case the development of hyperthyroidism or hypothyroidism. The drastic test conditions (e.g., hands and forearms were washed ten times for 2.5 minutes with povidone–iodine liquid soap within 5 hours) permit the conclusion that povidone–iodine preparations are nontoxic, at least for healthy adults.

In contrast, application of topical iodinated antiseptics in neonates (term and preterm) caused, besides a notable increase in urinary iodide excretion, significantly high levels of TSH that were interpreted as transient thyroid dysfunction (Vilain et al., 1994; Linder et al., 1997). In a large-scale study at an obstetric ward, it was found that iodine overload in the mothers, caused by skin disinfection before delivery using an iodophor preparation, induces a transient impairment of thyroid function in the infants, especially if they are breast-fed. Because this situation is detrimental to screening for congenital hypothyroidism, iodophor preparations are not recommended in obstetrics (Chanoine et al., 1988). All three author groups recommend that caution be exercised in the use of iodine-containing antiseptics in neonates, and that noniodinated substances with similar antibacterial efficacy should preferably be used.

However, in a prospective, controlled study, it was found that transient hypothyroidism is not a common sequela of routine skin cleansing with povidone–iodine in premature neonates in North America, an iodine-sufficient area (Brown et al., 1997). This result differs from the foregoing studies performed in Europe, which is generally considered an iodine-deficient area.

The irritation potential of povidone–iodine solutions was investigated by comparing subjective and objective assessment techniques with three similar formulations (all containing 10% povidone–iodine and variable amounts of potassium iodate: 0%, 0.03%, and 0.225%) that were applied for 1 to 8 hours to the skin (Dykes and Marks, 1992). The methods used, subjective assessment of erythema, objective measurement of skin color (erythema meter), and laser Doppler blood flow measurements, showed consistent results indicating a steady increase in cutaneous irritation, which in one case (the preparation with the highest level of potassium iodate) was essentially elevated. However, because these experiments were conducted with the povidone–iodine specimen occluded by an aluminum chamber, the results should not be extrapolated to normal conditions in which the povidone–iodine solution dries on the skin, forming a protective film with greatly reduced free iodine.

That povidone–iodine can evoke fatal consequences if misapplied was shown in a case report on surgical débridement of a hip wound where a patient died 10 hours after continuous postoperative wound irrigation with Betadine. Toxic manifestations of systemic iodine absorption appeared to be the cause of death (D'Auria et al., 1990).

With regard to the toxicity of topical preparations, the following generalizations can be made:

1. Because the stratum corneum of intact skin is an effective barrier against electrolytes (Goldsmith,

1983), it is penetrated by iodine in the form of molecular iodine, but not by iodide or triiodide.
2. In body cavities (e.g., during treatment of mucous membranes, perineal wash) that are not protected by a stratum corneum, however, the incorporation of iodide and triiodide also becomes important because iodine preparations always contain these species.
3. Depending on the chemical nature of the tissue—dry skin with a lower, or surfaces of body cavities with a higher reducing potential—the penetrating iodine is reduced more or less quickly to iodide.
4. The degree of irritation and the amount of total iodine absorbed by the body mainly depend on:
   a. The composition of the applied solution with regard to the concentrations of the main iodine species, I_2, I_3^-, and I^-
   b. The time of application
   c. The treated area
   d. The nature of the treated area (horny skin, mucosa)
   e. The physical condition (intact skin, open wounds)

   Long-term applications (irrigation) on open wounds with concentrated formulations (e.g., undiluted povidone–iodine preparations) should be avoided.
5. As long as it is not reduced, free iodine present on the skin diffuses not only into deeper regions but back out of the skin, resulting in a certain period of residual bactericidal activity on the skin surface (see later). The reduced portion, however, remains in the body for some time and gives rise to an increased level of serum iodide.
6. The incorporated iodine in the form of iodide and organically bound iodine (which comes to ~75% of the total resorbed iodine) leaves the body by urinary excretion and has a biologic half-life of approximately 2 days (Glöbel et al., 1984). This finding also suggests that the frequency of treatments (e.g., in case of burned skin) needs to be taken into account because it can provoke an unexpected accumulation.
7. If the mode of application of an iodine preparation is expected to cause a measurable increase in serum iodide, a change to another disinfectant is indicated for neonates and patients with disturbed thyroid function.

Ingestion of Iodinated Drinking Water

Although it has limited use in terrestrial applications, elemental iodine is considered to be an appropriate drinking water disinfectant on extended space flights because it does not present other hazards (e.g., chlorine gas or ozone) that are unacceptable in a confined space. It is already installed aboard the space shuttle and will also be incorporated into the water recovery and distribution system for the International Space Station (Atwater et al., 1996). In view of the known potential risks associated with elevated intake of iodine—in particular, congenital goiter—the effects of iodine and iodide on thyroid function in humans were investigated (Robison et al., 1998). The experiments failed to confirm the differential effect of I_2 on maintenance of serum T_4 concentrations relative to the effect of I^- that was observed in previous experiments in rats (Thrall, et al., 1992). However, based on elevations in TSH, the authors suggest some concern over the potential impact of chronic consumption of I_2 in drinking water.

PRACTICAL APPLICATIONS

Human Medicine

The most important application of iodine in human medicine is in the disinfection of skin, which has been in use since the mid-19th century (Horn et al., 1972). In addition to prophylaxis (e.g., preoperative preparation of the skin, surgical disinfection of hands, disinfection of the perineum), iodine preparations are used for therapeutic purposes (e.g., treatment of infected and burned skin). The oldest account of the therapeutic use of iodine dates to 1829: *Mémoire sur l'emploi de l'iode dans les maladies scrofuleuses* (Lugol, 1829).

The high-level aqueous and alcoholic iodine preparations used up to the 1960s have been replaced, to a great extent, by the iodophors because of fewer unwanted side reactions (see Iodophores). Among the investigated iodophors, povidone–iodine is usually considered the compound of choice (Knolle, 1975). However, the initial enthusiasm for this compound was curtailed by observation of intrinsic bacterial contamination of a 10% povidone–iodine preparation (Pharmadine) by *Pseudomonas cepacia,* leading to an outbreak of pseudobacteremia in a hospital (Craven et al., 1981). Another surprising feature was the increased bactericidal activity of dilute povidone–iodine preparations (Berkelmann et al., 1982). These events initiated a thorough study of the physicochemical fundamentals of povidone–iodine (Horn and Ditter, 1984; Gottardi, 1983) and the articulation of the importance of galenics in the microbicidal efficacy of povidone–iodine solutions (Pinter et al., 1983). Attempts also were made to replace the povidone carrier with other macromolecules that might be even more harmless than povidone, which, after all, has been used as a blood substitute. In this connection, polymers constructed of sugar molecules (e.g., polydextrose) are of great interest. When rigid aseptic precautions are required and no painful irritations are to be expected, however, iodine tincture is still used as the strongest iodine-based disinfectant. A detailed review of the use of iodine in human medicine is given by Knolle (1975), and a good historical account and description of aqueous solutions of iodine and tincture is given by Reddish (1957).

Iodine has also been used for the disinfection of medical equipment, such as catgut, catheters, knife blades, ampules, plastic items, rubber goods, brushes, multidose vials, and thermometers (Gershenfeld, 1977). Disinfection with iodine, however, is not appropriate for every sort of material. Many metal surfaces, in particular, are not resistant to oxidation and can be altered. Furthermore, some plastics absorb elemental iodine, causing a brownish staining that fades very slowly, if at all.

Veterinary Medicine

Disinfection of the cow's udder with iodine before and after milking is a widely adopted application, which started in 1958 when it was found that dipping teats in 0.1%, 1%, and 2.5% tinctures of iodine markedly reduced the numbers of staphylococci that were recovered from milking machine liners (Newbould and Barnum, 1958). Today it is performed in general by using iodophoric preparations with 0.25% to 1.0% available iodine. This treatment is well tolerated and reduces the incidence of intramammary infections caused by *Streptococcus* and *Staphylococcus* pathogens common around dairies (Boddie and Nickerson, 1997; Boddie et al., 1997). With regard to the possible contamination of milk with iodine, however, contamination would seem to be less likely with a preparation containing low concentrations of total iodine. An example is the animal drug IodoZyme, an EBI powder concentrate that produces on dissolution 500 ppm total iodine with 150 ppm I_2 (West Agro, Inc., 1995). The manufacturer claims that it is as effective as conventional 0.5% iodine teat dip (based on povidone–iodine), but contains only the tenth part of total iodine compared to the latter.

Disinfection of Water

Drinking Water

The first known field use of iodine in water treatment was in World War I by Vergnoux (White, 1972), who reported rapid sterilization of water for troops. Since that time, several studies (White, 1972) have shown that iodination is suitable for the disinfection of drinking water, especially in emergency situations. Of considerable importance is the work of Chang and Morris (1953), which led to the development of the tetraglycine hydroperiodide tablets (Globaline) that have been successfully used to disinfect small or individual water supplies in the U.S. Army. This method of water purification (addition of iodine tablets or calcium hypochlorite to the water, followed by a 25- or 30-minute disinfectant contact period before drinking) is still used by the U.S. Army. The Travelers Medical and Vaccination Center (1999) claims that chemical disinfection using iodine (Potable Aqua tablets) is more reliable for water purification than chlorine or silver. Because the killing effect of iodine depends on temperature, they recommend the following standing times: 60, 30, and 15 minutes at 5°C, 15°C, and 30°C, respectively (one iodine tablet for 1 L of water).

The use of iodine for water disinfection involves some potential health risks because the chemicals carrying out the disinfection are not removed during these procedures (Schaub, 1986). On the other hand, it was demonstrated in two prison water systems that iodine in doses up to 1.0 ppm is sufficient for disinfection, does not produce any discernible color, taste, or odor, and has no adverse effect on general health or thyroid function. Thomas et al. (1978) reported a 15-year pilot project in which they observed no instances of ill effects caused by use of iodine for water disinfection. The authors found that iodination is an effective and economic means of water purification, of particular advantage in rural and underdeveloped countries. More recently, the iodine resins have been successfully used as a basis for purifier units that, as long as they are not exhausted, work very well, bringing about a kill of 4 logs. For emergencies and for travelers, "pocket purifiers" have been developed whose performance was officially approved through registration by the U.S. Environmental Protection Agency (Regunathan and Beauman, 1986). A description of iodine-containing ion exchange resins for point-of-use water, including a new resin type that provides a more consistent and controllable level of iodine, was given by Osterhoudt (1997). For the disinfection of the drinking water supplies aboard spacecraft, iodine was chosen because of its low risk potential compared with ozone or chlorine. For the Skylab mission, it was furnished by a 30 g/L stock solution containing KI and I_2 in a 2 : 1 molar ratio, whereas for the space shuttle program, a new device for the controlled release of I_2 was introduced, the microbial check valve, consisting of a canister containing iodinated strong base ion exchange resin packed with polyiodide anions (I_3^-, I_5^-, I_7^-) (Atwater et al., 1996).

Swimming Pool Water

Compared with chlorine, iodine has the advantage that it virtually does not react with ammonia or other nitrogenous compounds and therefore produces no compounds that are likely to contribute to swimmers' discomfort in the form of eye irritation or obnoxious odors (Black, 1961). The use of iodine in swimming pool disinfection has the following advantages (Putnam, 1961): (a) an approximately one-third savings on chemical cost, (b) no disagreeable odor or taste, (c) no irritation of the mucous membranes, (d) good disinfection of swimming pool water, (e) no danger in storage or use because the material is in crystalline form, (f) the residual is stable and does not fluctuate quickly, (g) the pH is stable after balance is reached, and (h) the swimmers' comfort is enhanced.

On the other hand, iodine is a notoriously poor algicide, and the control of algae growth requires additional measures. Probably the most serious flaw in the use of iodine

is the difficulty in controlling the color of the pool water, particularly in the presence of a large amount of iodide, which generates a yellowish-brown color (generated by I_3^- ions). The problem of color control plus its inability to control algae all but eliminate iodine from use by the swimming pool industry (White, 1972). In the 1990s, no important contributions to this topic have been made.

Wastewater

Only a few contributions deal with the use of iodine in the disinfection of water that, in contrast to drinking and swimming pool water, do not come in direct contact with humans (e.g., wastewater and industrial water). Because these waters in general are highly charged with dissolved nitrogenous substances (proteins and their hydrolysis products), the use of iodine, which does not react with nitrogen compounds, should confer great advantages.

For applications that range in technical dimensions, however, the question of costs also must be considered, and because iodine is nearly three times as expensive as chlorine per mole, the advantages and disadvantages of iodine must be weighed carefully. In a study of disinfection with a mixture of I^- and NH_2Cl that generates elemental iodine, Kinman and Layton (1976) found that this system offers considerable potential for use in water disinfection for potable water, industrial water, and water that must be discharged to shellfish areas. Investigating alternatives to wastewater disinfection in pilot plant studies, Budde et al. (1977) compared the disinfectants chlorine, ozone, and iodine and found that for the same level of fecal coliform destruction, iodine was the most expensive under all conditions studied. Nevertheless, some recent innovations have been presented that are maintaining the use of iodine in this field. Besides an electrolytic approach (Sampson and Sampson, 1995), a method using solid iodine as a source has been published (Harvey et al., 1998). In both cases, the resulting diluted iodine solution is recommended for disinfection of cooling tower water, sewage, and wastewater.

The suitability of iodine for the food processing industry, particularly as iodinated ice for fish and fish product preservation, is also claimed (Harvey et al., 1998). This contribution is the only one for iodine that relates to the field of *preservation,* as another issue of this text.

Disinfection of Air

Since Lombardo (1926) first advocated the use of iodine as an aerial disinfectant, experiments on the disinfection of air have been carried out, mainly during World War II. Plesch (1941) recommended the aerial disinfection of air raid shelters with iodine vapors as a prophylactic measure against influenza. White et al. (1944) reported iodine to be effective as an aerial disinfectant at concentrations much below its saturation vapor pressure, and Raymond (1946) found a "relatively tolerable" concentration of 0.1 mg/ft^3 (3.5 mg/m^3) to be sufficient for a rapid kill of freshly sprayed salivary organisms. However, the danger that iodine vapors pose to the respiratory organs must be kept in mind, as documented by the fact that the maximum allowed concentration of iodine is 1.0 mg/m^3 (threshold limit value; Lewis and Sweet, 1986), which is less than one third of the concentration recommended by Raymond (1946). In spite of this drawback, iodine-based procedures have been proposed recently (mainly in East Asia) that aim to disinfect air by iodine-containing wall coatings (Suzuki, 1998), ceramics loaded with iodine (Okubo, 1997), and vaporizing solutions containing iodine, among other constituents (Na and Fan, 1994; Huang and Zhu, 1993).

RESIDUAL EFFECTS OF IODINE PREPARATIONS

The aforementioned back-diffusion of the nonreduced portion of the absorbed iodine, which takes place much more slowly than uptake, was not recognized until comparatively recently (Gottardi, 1995). By means of a photometric method, this iodine flux (dim = mass/area × time) has been ascertained on the skin after application of Lugol's solution and povidone–iodine preparations with various concentrations of free iodine. The most important findings are the following: the intensity of the iodine flux depends on the amount of iodine absorbed by the skin, which increases with the concentration of free iodine of the applied solution and the time of application. Applying Lugol's solution (155.6 ppm free iodine) for only 1 minute, the flux could be detected for approximately 24 hours (range: 50 to 0.005 μg I_2/cm^2/minute), whereas after application of a povidone–iodine preparation (10 ppm free iodine) for 3 to 5 minutes, the flux was detectable for 0.5 to 1 hour (range: 0.2 to 0.005 mg I_2/cm^2/minute). The latter result suggests that even the application of iodophor preparations could give rise to a persistent (residual) microbicidal action. This has been proved by comparing the surviving colony-forming units of *Micrococcus luteus* (applied to the skin by artificial contamination) on normal skin with those on skin that was treated for 5 minutes with a povidone–iodine preparation (10 ppm free iodine) immediately before contamination. A logarithmic reduction rate of 0.4 was found, a result that confirmed the bactericidal action of the iodine diffusing out of the skin. As long as iodine diffuses out of the skin, active disinfection from the inner regions of the skin takes place, and an effective action on the residential pathogens can be expected, a feature that seems to be unique in the field of skin disinfection.

In this regard, Hartmann (1985) found by a special method that the reduction of the total resident flora was significantly higher using povidone–iodine than with isopropanol. This is in contrast to the usual findings, mainly

in testing preparations for surgical hand scrubs, which in general exhibit a better degerming activity of alcohols (Rotter, 1996).

RANGE OF ACTION

Iodine is an excellent, prompt, effective microbicide with a broad range of action that includes almost all of the important health-related microorganisms, such as enteric bacteria, enteric viruses, bacterial viruses, and protozoan cysts (Hoehn, 1976). Mycobacteria and the spores of bacilli and clostridia can also be killed by iodine (Wallhäusser, 1978). Furthermore, iodine also exhibits a fungicidal and trichomonicidal activity (Knolle, 1975). As is expected, varying amounts of iodine are necessary to achieve complete disinfection of the different classes of organisms. Within the same class, however, the published data on the disinfecting effects of iodine correspond only to a small extent. In particular, the published killing times for spores (Wallhäusser, 1978) and viruses (Knolle, 1975) are widely disparate. One reason for this might be the nonuniform sensitivity of microorganisms to iodine, which applies not only to the type of organism but to the growth conditions.

Pyle and McFeters (1989) demonstrated that bacterial isolates (predominantly *Pseudomonas* species) from water systems disinfected by iodine showed differences (which did not always have the same sign, however) of up to 4 logs decrease in CFUs after contact with iodine (1 mg/L, pH 7, 1 minute) depending on whether they were grown in brain–heart infusion or in phosphate buffer. A similar result was attained with *Legionella pneumophila,* which also showed a differing susceptibility to iodine with cultures grown in well water, on rich agar media, or attached to stainless steel (biofilm). Water cultures of legionellae associated with stainless steel surfaces were 135 times more resistant to iodination than were unattached legionellae, and were 210,000 times more resistant to iodination than were agar-grown cultures (Cargill et al., 1992). Both studies indicate that growth conditions can dramatically affect susceptibility to iodine (and other disinfectants) and must be considered when evaluating the efficacy of a disinfecting agent.

As mentioned by Hoehn (1976), comparison of previously published references concerning the effectiveness of disinfection processes for different microorganisms are difficult because of the myriad different environmental conditions under which experiments are conducted (e.g., pH value, temperature, concentration and type of iodine preparation, time of exposure to the disinfectant, and amount and type of dissolved organic and inorganic substances). Another problem is the fact that, in general, most of these conditions are not described in detail, and an exact comparison of the germicidal effectiveness of iodine against different organisms, as well as a comparison with the other halogens, is therefore practically impossible. In spite of these difficulties, some authors have tried to summarize the disinfecting properties of iodine and the other halogens by reviewing the literature and analyzing the existing data. The most important conclusions are:

- A standard destruction (i.e., a 99.999% kill in 10 minutes at 25°C) of enteric bacteria, amoebic cysts, and enteric viruses requires I_2 residuals of 0.2, 3.5, and 14.6 ppm, respectively (Chang, 1971).
- On a weight basis, iodine can inactivate viruses more completely over a wide range of water quality than other halogens (Krusé et al., 1970).
- In the presence of organic and inorganic nitrogenous substances, iodine is the cysticide of choice because it does not produce side reactions that interfere with its disinfecting properties (Krusé et al., 1970).
- Iodine requires the smallest dosage (in milligrams per liter) compared with chlorine or bromine to "break any water" to provide a free residual (Krusé et al., 1970).
- I_2 is two to three times as cysticidal and six times as sporicidal as HOI, whereas HOI is at least 40 times as virucidal as I_2. This behavior is explained on the one hand by the higher diffusibility of molecular iodine through the cell walls of cysts and spores, and on the other hand by the higher oxidizing power of HOI (Chang, 1971).
- For some microorganisms, iodine resistance also has been ascertained (e.g., *Pseudomonas alcaligenes* and *Alcaligenes faecalis*), which can account for the bulk of the microbial flora in iodinated swimming pools (Favero and Drake, 1966). Other studies, however, are showing that iodine does not induce resistance in isolates of *Pseudomonas, Klebsiella, Enterobacteria, E. coli*, and other species (Hingst et al., 1995; Reimer et al., 1998).
- Because disinfection is a chemical reaction, the influence of temperature on reaction speed—as a rule of thumb, lowering the temperature approximately 10°C halves the speed—must be considered for microbicidal events in such a way that either the contact time or the concentration of the disinfectant is increased if cold water is to be treated. The lack of efficiency at low temperatures was demonstrated by Regunathan and Beauman (1986), who showed that some iodine preparations designed to purify canteen water worked well against *Giardia* at 20°C but not at 3°C if used according to the instructions.
- With regard to culture conditions, iodine (1,500×) exhibits a greater difference in CM·t values (concentration in molarity multiplied by time in minutes to achieve 99% decrease in viability) than chlorine (68×) against water-cultured and agar-grown legionellae. Iodine was 50 times more effective than chlorine against agar-grown cultures, but was only twice as effective when tested against water-grown legionellae cultures (Cargill et al., 1992).

A survey of concentration, exposure time, and disinfective results in practical applications of iodine is given in Table 8.2.

ACRONYMS AND ABBREVIATIONS

CFU colony-forming units
EBI enzyme-based iodine
T_4 tetraiodothyronine (thyroxine)
T_3 triiodothyronine
TSH thyrotropin
USP United States Pharmacopoeia

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